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THE METABOLISM OF THE RADIOACTIVE ELEMENTS CREATED BY NUCLEAR FISSION*

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THE appearance of new agents that carry with them a potential menace to the health and security of the public is bound to be accompanied by a very understandable attitude of fear. The highly dramatic introduction to the world at large of the release of atomic energy has produced an unprecedented degree of concern for public safety. Frequently, the concern expressed has assumed the proportion of panic owing to the lack of sufficient basic information on the part of those presenting their evaluations of the problems posed by this twentieth-century version of Pandora's box.

For example, considerable apprehension has been displayed concerning the disastrous effects that might follow the contamination of an inhabited area as the result of an underwater or subsurface explosion of an atomic bomb, which of course would release very large quantities of the radioactive fission products. There is no question that this type of action would serve to contaminate a considerable area to a dangerous degree. However, it is highly important that the inhabitants in the immediate vicinity realize that they are not all going to acquire the atomic-age version of the fate of the radium-dial painters; moreover, it is appropriate that steps be taken to keep to a minimum the incidence of radioactive poisoning after such an episode. Should such a problem ever arise, information and instruments are in hand to approach it intelligently and with a gratifying degree of effectiveness.

The work described in this article is but a small part of the many phases of the medical research activities within the atomic-energy program,‡ which were initiated during the war by the Manhattan Project and are now being continued by the Atomic Energy Commission. Space does not permit even a partial enumeration of the many fields of investigation that are relevant to the medical aspects of the release of nuclear energy. It is important to indicate that these manifold activities are continuously accumulating the knowledge necessary to ensure the protection of the nation against the hazards inherent in the widespread development and applications of atomic energy. It is pertinent to recall that throughout the entire wartime period of activity of the Plutonium Project, there was not a single known episode of manifest radiation injury to the thousands of persons who worked on this program. The extent of scientific information, the number of trained and experienced personnel, and the availability of instruments for the detection of radioactivity is at a far higher level than is commonly supposed. Thus, the necessary safeguards for the peacetime applications of atomic energy are keeping pace with the rapid progress of this new field. At the same time the security of the nation has been strengthened against the possible consequences of military action in the event of an international disaster.

The phenomenon of nuclear fission in both the controlled release of atomic energy in the chain-reacting uranium pile and the instantaneous detonation of an atomic bomb is associated with the immediate emission of very energetic and penetrating neutrons and gamma rays. If an appreciable quantity of the fissionable element, such as uranium or plutonium, undergoes fission, a radioactive residue is left. This is due to the fact that the two atomic nuclei produced by the cleavage of a uranium or plutonium nucleus are unstable and thus radioactive. For this reason the radiation from either a chain-reacting pile or an atomic bomb continues after fission has ceased. These radioactive fragments from the fission of uranium and plutonium are called fission products and include radioactive isotopes of 34 different elements extending from zinc to the rare earth europium.[1] The explanation for the large number of different elements produced by fission is that the fissioning nucleus does

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not divide into two equal parts but rather splits into nuclei of varying sizes. The fissionable element employed in the present chain-reacting piles is uranium, and coincidental to the formation of the fission products is the production of neptunium, which is the radioactive parent of plutonium.[2] Thus, the menace of radiation from the release of nuclear energy is not limited to the duration of the fission reaction but continues on afterward. The relative intensity of radioactivity arising from nuclear fission decreases with time, owing to the fact that the fission products are composed of a mixture of a large number of radioactive isotopes whose half lives range from a fraction of a second to almost a million years. The mixture of fission products emits both beta rays and penetrating gamma rays. The quantities of these radioactive substances that are created are enormous. The large chain-reacting piles at Hanford are operated to produce plutonium. This requires that after an appropriate interval the uranium in the pile be removed and plutonium isolated from the uranium and accompanying fission products by a very elaborate and complicated series of chemical processes. These piles produce plutonium in kilogram quantities, and at the same time a comparable mass of fission products is created. The quantity of radioactivity of the fission products with moderately long half lives falls in the range of hundred of millions of curies. The magnitude and potential dangers associated with this program become apparent when one makes a comparison to the history of the radium industry. Up to the time of World War II there had been isolated about 1 kilogram of radium, which possesses by definition 1000 curies of radioactivity. A large number of cases of radium poisoning had been reported, notably in the luminous-dial industry, a considerable proportion of which terminated fatally.

Radioactive substances can produce injury either by external or by internal radiation of the body. Of the two, the potentialities for injury are greater if the radioactive substance is within the body. The history of the circumstances surrounding the radium industry is illustrative of the point, for it appears fairly certain that the preponderance of fatal injuries arose from internal irradiation rather than external exposure. The medical program of the Plutonium Project, which was created during the war years under the direction of Dr. R. S. Stone, was faced with the responsibility of protecting the personnel against quantities of radioactivity that were of the order of a millionfold greater than had been encountered by the radium industry over a period of half a century. Here the problem had to be met quickly in the haste of wartime urgency for the thousands of scientists and technicians working on the Atomic Energy Project. One of the many research programs that arose from these needs was a survey of the metabolism of the various elements created by the release of nuclear energy. A summary of a portion of this work is presented here, and more detailed accounts of these and related studies have been published elsewhere.[3-6]

It is appropriate to mention a few of the salient factors involved in the problem of radioactive poisoning, for it was these considerations that shaped the pattern of the research to be described. To evaluate a potential hazard of a given radioactive element, it is necessary to consider the half life, radiation characteristics, route of entry into the body, assimilation, distribution, retention, excretion and relative susceptibility of the different organs or tissues to the radiations emitted by the deposited material. Radiation injury, both acute and chronic, is a function of the intensity of the irradiation and the duration of the exposure to the irradiation. A radioactive substance, either as an element or as a compound, may enter the body by one or more of four routes — namely, the lungs, the digestive tract, through cuts or abrasions, and the intact skin. Once the material has been absorbed, regardless of the portal of entry, it will be distributed to the many tissues of the body, where it will be taken up in widely varying concentrations and be retained for different intervals. The degree of injury will vary with the character of the radiation and the radiosensitivity of the irradiated organ or tissue. For example, alpha particles are relatively more destructive to most living tissue than beta or gamma rays, when the biologic effects are compared on the basis of equivalent amounts of total ionization in the tissue. Concerning variations in vulnerability to radiation, the bone marrow, which is the center of hemopoiesis, is very sensitive, whereas structures such as liver, brain and muscle are relatively radioresistant.

If the assimilation, distribution, retention and excretion of a given radioelement are determined, it is possible to make an estimate of the amount of exposure to such a substance that might be expected to produce either acute or chronic injury. If the tracer or metabolic studies are done in animal experiments, as in the investigations described below, a variable is introduced by the extrapolation of such results from the animals to man. However, in most instances this error is probably not significantly greater than individual variations between different human beings in their response to a novel biologic experience such as is offered to the body by most of the radioelements associated with the release of nuclear energy.

The available information was very limited at the time of the inception of the Plutonium Project concerning the metabolic properties of the elements whose radioactive isotopes arise from fission. Among the 34 different fission-product elements there are 14 whose radioactive isotopes possess half lives ranging from days to years and are produced in relatively high abundance by the fission process.

Almost all the total radioactivity arising from the fission-product mixture after it has decayed for a week is contained in the radioactive isotopes of these 14 elements, which are listed in Table 1. These elements possess metabolic patterns that differ not only from radium but also, in most instances, from one another. Prior to 1942, only one of this group, radioiodine, had received sufficient attention regarding its metabolic properties to permit a reasonable evaluation of the amount that could be tolerated in the body without producing manifest injury.[7] A second fission product, radiostrontium, had been subjected to some investigation before this time but not in enough detail to satisfy the requirements of the medical research program of the Plutonium Project.[8, 9] The remaining 12 fission products and strontium, as well as neptunium and plutonium, were subjected to tracer studies so that their potential capacity to produce injury as internal radioactive poisons to those exposed to these substances could be predicted.

These tracer studies included a survey of the metabolism of the fission products in the carrier-free state,* and neptunium and plutonium in the rat after oral ingestion, inhalation and parenteral injection. The fourth possible route of entry — namely, the passage through the intact skin — was not investigated. The absorption, distribution, retention and excretion were investigated with each substance for the three channels of administration. Extensive radioautographic studies were made of organs in which a high degree of selective localization and retention took place, that a correlation might be established between the accumulation of the radioelement and the microscopical anatomy of the tissue.

The animals were killed at regular intervals after administration of each radioelement. Twelve to fifteen organs and tissues were removed, and their radioactivity determined, as well as the fraction eliminated in the excreta. The usual intervals before the animals were killed after receiving the radioactive materials were one, four, sixteen and sixty-four days. In a number of instances the experiments were extended to intervals of one hundred and twenty-eight and two hundred and fifty-six days. In several of the studies it was necessary to conclude the experiments prior to the sixty-four-day interval owing to the relatively short half lives of several of the radioisotopes employed.

The most significant metabolic characteristics of the fission products, and of neptunium and plutonium, are listed in Table 1. It will be noted that 8 of the fission products, as well as neptunium and plutonium, are not absorbed to any significant

TABLE 1. *Summary of the Metabolism of the Principal Members of the Long-Lived Fission Products and Neptunium and Plutonium in the Rat after Parenteral and Oral Administration.*

RADIOELEMENT	HALF LIFE	FISSION YIELD	ORAL ABSORPTION	ACCUMULATION IN PRINCIPAL ORGAN OF RETENTION	RATE OF ELIMINATION FROM PRINCIPAL ORGANS OF RETENTION
		%	%	%	
Strontium					
Sr^{89}	53.0 days	4.6	5–60	70 (bone)	>200 days (bone)
Sr^{90}	25.0 yr.				
Barium					
Ba^{140}	12.8 days	6.1	5–60	60 (bone)	>50 days (bone)
Iodine					
I^{131}	8.0 days	2.8	100	20 (thyroid gland*)	>30 days (thyroid gland*)
Cesium					
Cs^{135}	33.0 yr.	—	100	45 (muscle)	15 days (muscle)
Yttrium					
Y^{91}	57.0 days	5.9	< 0.05	65 (bone)	>500 days (bone)
				70 (liver)	10 days (liver)
Lanthanum					
La^{140}	40.0 hr.	6.1	< 0.05	30 (bone)	>25 days (bone)
Cerium					
Ce^{141}	28.0 days	5.7	< 0.05	50 (liver)	10 days (liver)
Ce^{144}	275.0 days	5.3	0.05	25 (bone)	100 days (bone)
				35 (liver)	10 days (liver)
Praseodymium					
Pr^{143}	13.8 days	5.4	< 0.5	50 (bone)	>100 days (bone)
				55 (liver)	10 days (liver)
Element 61					
61^{147}	3.7 yr.	2.6	< 0.05	35 (bone)	>100 days (bone)
Zirconium					
Zr^{95}	65.0 days	6.4	< 0.05	35 (bone)	>100 days (bone)
				30 (bone)	30 days (bone)
Columbium					
Cb^{95}	37.0 days	6.4	< 0.5	25 (blood)	1 day (blood)
Ruthenium					
Ru^{103}	42.0 days	3.7			
Ru^{106}	1.0 yr.	0.5	< 0.05	3.5 (kidneys)	20 days (kidneys)
Tellurium					
Te^{127}	90.0 days	0.033	25.0	15 (blood)	15 days (blood)
Te^{129}	32.0 days	0.19	25.0	6 (kidneys)	15 days (kidneys)
Xenon					
Xe^{133}	5.3 days	4.5	Distribution proportional to fat content of body; half time in body, 2 hr.		
Neptunium					
Np^{239}	2.2 days	—	< 0.05	65 (bone)	>50 days (bone)
Plutonium					
Pu^{239}	2.2×10^4 yr.	—	0.007	75 (bone)	>2 yr. (bone)

*Human studies.[7]

*The term carrier-free signifies that the radioelement was not diluted with measurable quantities of the stable nonradioactive form of the same element.

degree by way of the digestive tract. After parenteral administration over half the fission-product group, as well as neptunium and plutonium, are accumulated by the skeleton and eliminated from this organ very slowly. The 5 members of the listed fission products that are absorbed from the digestive tract are strontium, barium, tellurium, iodine and cesium. Xenon is readily and rapidly absorbed from the lungs after inhalation and is as readily eliminated from the lungs. Strontium and barium are deposited and retained to a high degree

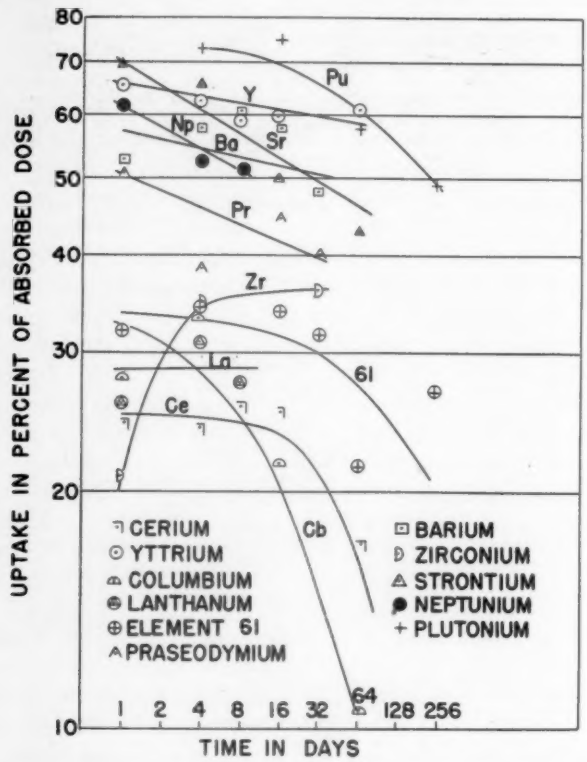

FIGURE 1. *Deposition of Carrier-Free Fission Products and Neptunium and Plutonium in the Skeleton of the Rat after Parenteral Administration.*

by the skeleton. Iodine is accumulated and retained by the thyroid gland. Tellurium exhibits some deposition in the kidneys and blood, with a rapid rate of release from these organs. Cesium is distributed quite uniformly throughout all the tissues, the greatest accumulation occurring in the muscle, and is quite promptly excreted. The patterns of distribution of strontium, barium, tellurium, iodine and cesium in the body after oral and pulmonary absorption are indistinguishable from their metabolism after parenteral administration. With the exception of ruthenium, the remainder of the listed fission-product series, as well as neptunium and plutonium, show a considerable accumulation and varying degrees of retention by the skeleton as shown in Figure 1. In lanthanum, cerium, praseodymium and element 61, there is an initially high degree of accumulation by the liver, but they are quite rapidly excreted from this organ, presumably by way of the bile. It will be noted from Table 1 that with the exception of columbium^{95}, and possibly strontium^{90}, cerium^{144} and 61^{147} the rates of elimination of the different fission products accumulated in the skeleton are less than their rates of radioactive decay. The fission products that fall into this category include strontium^{89}, yttrium^{91}, zirconium^{95}, barium^{140}, lanthanum^{140}, cerium^{141} and praseodymium^{143}. With the exception of iodine in the thyroid gland, the remainder of the fission products listed in Table 1 — namely, ruthenium^{103}, ruthenium^{106}, tellurium^{127}, tellurium^{129}, xenon^{133} and cesium^{135} — are rapidly excreted and at rates considerably greater than their half lives.

The rates of elimination from the skeleton of neptunium and plutonium are quite slow. The daily excretion of plutonium in the rat falls to 0.01 per cent of the amount remaining in the body a year after the intramuscular administration of this radioactive element. Since neptunium^{239}, which is the principal radioisotope of this element produced in the chain-reacting pile, has a half life of only two days, it is not possible to observe its rate of excretion after an extended interval. However, it is obvious that its rate of elimination from the skeleton is far less than its rate of radioactive decay.

Radioautographic studies were made of the distribution of the radioactive isotopes of strontium, zirconium, columbium, cerium, element 61 and plutonium in 5-micron sections of undecalcified rat femurs.[8, 10, 11] The metabolism of strontium in the skeleton is very similar to that of calcium and, as might be expected, the radioautographs revealed that the accumulated radiostrontium in the femur was fairly evenly distributed throughout the mineral structure of the bone in young rats (Fig. 2). It is assumed that the same results would be observed with barium, which possesses very similar chemical properties to those of strontium and whose metabolic characteristics are indistinguishable from those of strontium under the experimental conditions of these studies. The other radioelements studied by this technic revealed a startling deviation from the pattern of distribution observed with radiostrontium. Plutonium exhibits this phenomenon to a marked degree, and from Figure 3 it may be seen that most of this element is apparently deposited in the periosteum and endosteum, and in the region of the trabecular bone. These results suggest that plutonium in the trabecular structure is not incorporated within the mineral structure of the bone but rather is deposited in the covering of the trabeculae. The pattern of distribution in the

bone of zirconium, columbium, cerium and element 61, as studied by this technic, resembles quite closely in most regards that observed with plutonium. A spotty distribution of cerium and element 61 has been observed within the cortical bone, which is believed to represent accumulation in the region of the small blood vessels. A similar effect is predicted for lanthanum and praseodymium in view of their closely related chemical and metabolic properties. A representative example of this pattern is shown for element 61 in Figure 4. The results obtained by the radioautographic studies suggest that the accumulation of these elements in the skeleton occurs in the superficial layers of the bone structure, and very possibly they are combined with proteins rather than being directly incorporated into the inorganic bone

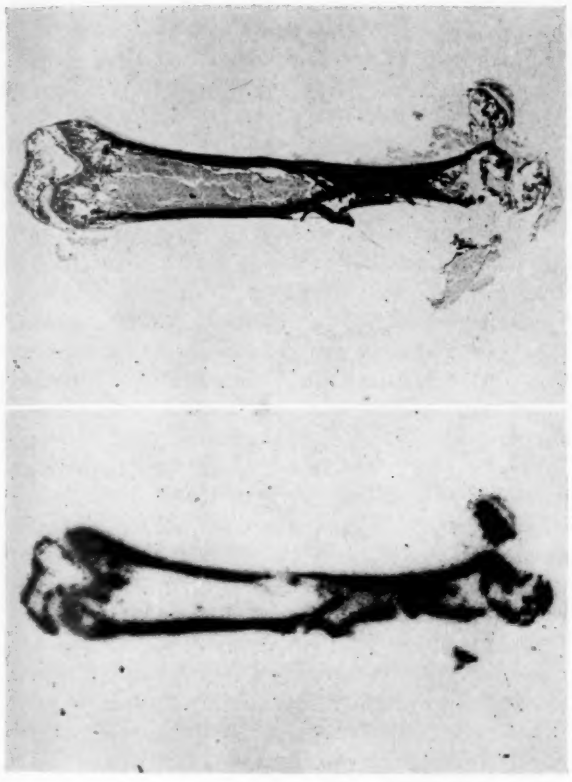

FIGURE 2. *Section of the Undecalcified Femur (Upper Photograph) and Corresponding Radioautograph (Lower) from a Young Rat that Had Received Radiostrontium One Week Before Death.*
Note the even deposition of radiostrontium throughout the mineralized structure of the shaft and the calcifying trabeculae beneath the epiphyseal plate (silver nitrate, hematoxylin and eosin stain x 3).

salts as is apparently the case with strontium and presumably barium. It is noteworthy that the distribution pattern for this group of elements, which are laid down so differently in the skeleton from strontium, apparently does not appear to change significantly with time in the adult rat. Radioautographs from adult female rats that had received plutonium nearly a year before they were killed showed no significant differences in distribution in the bone when compared to bone radioautographs

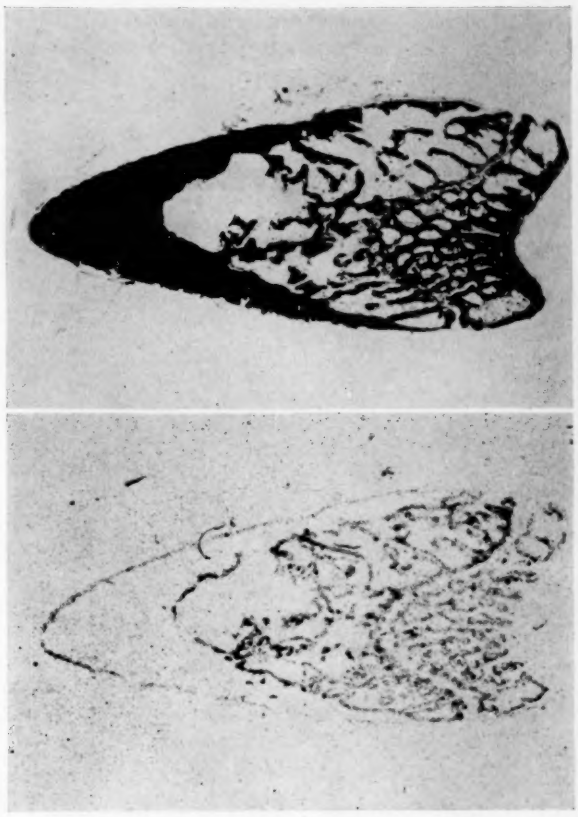

FIGURE 3. *Section of the Undecalcified Femur (Upper Photograph) and the Corresponding Radioautograph (Lower) from an Adult Rat That Had Received Plutonium One Week before Death.*
Note the superficial deposition of plutonium on the surfaces of the shaft and trabeculae, and the absence of plutonium from epiphyseal cartilage (silver nitrate, hematoxylin and eosin stain x 8).

from animals killed a few days after the administration of this radioelement.

The direct introduction into the lungs of soluble compounds of the carrier-free fission products, and neptunium and plutonium, demonstrated that the radioelements that were not absorbed from the digestive tract were retained by the lungs to a considerable degree for a prolonged interval.[4] Fission products exhibiting these characteristics included yttrium, zirconium, columbium, ruthenium, lanthanum, cerium and praseodymium. Although these pulmonary studies were not conducted with element 61, it is assumed that its behavior would be comparable in view of its other metabolic properties, which are closely akin to the group of substances named above. The same phenomenon was

observed with neptunium and plutonium. Radioautographs demonstrated that the deposited radioactive materials were distributed throughout the lungs, including structures below the ductus alveolaris. No accumulation in the bronchial tree, lymph nodes or blood vessels was noted even after several months. Some absorption took place through the lungs for all the substances retained by this organ, and, except for ruthenium, most of the absorbed material was deposited in the skeleton, as would be expected from the parenteral metabolic studies. Fission products that are absorbed through the digestive tract — notably, strontium, barium, tellurium, iodine and cesium — were found to be quite readily absorbed through the lungs.

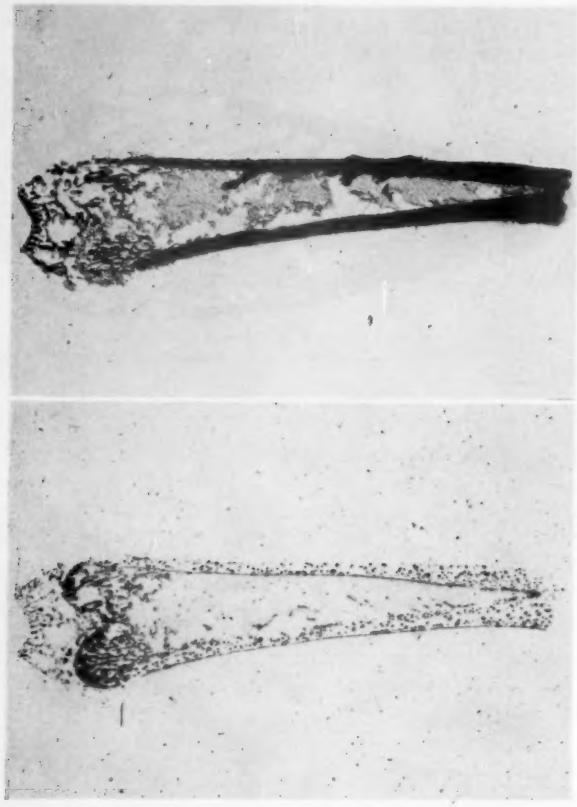

FIGURE 4. *Section of the Undecalcified Femur (Upper Photograph) and Corresponding Radioautograph (Lower) from an Adult Rat that Had Received Element 61 Four Days before Death.*

Note the superficial deposition of this radioactive element on the surfaces of the shaft and trabeculae. The spotty areas of accumulation within the shaft are believed to be depositions of element 61 in the immediate vicinity of the small blood vessels in the cortical bone (silver nitrate, hematoxylin and eosin stain x 3½).

These experiments, which were quite qualitative in character, were later supplemented by a large series of aerosol studies using several different compounds of plutonium and a mixture of carrier-free fission products.[12,13] The inhalation of these different radioactive aerosols was followed by the initial retention of approximately 75 per cent of each material. The retention was almost equally divided between the lungs and the upper respiratory tract (Fig. 5). The material in the upper respiratory tract was rapidly removed, presumably by ciliary action, and appeared in the feces, and the fraction remaining in the lungs was eliminated quite slowly. Eight months after exposure to a plutonium oxide aerosol, which is an insoluble compound of the element, 4 per cent of the total quantity inhaled still remained in the lungs. Comparable values were observed with plutonyl nitrate, a soluble compound of the element, and with the long-lived fission-product mixture. There was very little absorption from the lungs, and subsequent deposition in the skeleton, after inhalation of the plutonium oxide and fission-product aerosols in an insoluble form. However, nearly 10 per cent of the plutonium, when inhaled as an aerosol of the soluble plutonyl nitrate, was absorbed through the

FIGURE 5. *Section of the Lung (Upper Photograph) and Corresponding Radioautograph (Lower) from a Rat Killed Immediately after the Inhalation of a Plutonium Oxide Aerosol. Note the deposition of plutonium on the walls of the bronchi and throughout the alveolar structure (hematoxylin and eosin stain x 4).*

lungs in the first twenty-four hours and deposited in the skeleton. From the qualitative data obtained from tracheal-intubation studies using soluble compounds of the individual fission products, and the plutonyl nitrate aerosol experiments, it appears probable that the inhalation of aerosols of soluble compounds of all fission products, and neptunium, would result in a significant degree of absorption from the lungs.

Radioautographs of pulmonary tissue from the aerosol studies revealed that, immediately after inhalation, the active material was deposited in both the bronchial tree and the structures below the respiratory bronchioles. Within a day the material in the bronchial tree had vanished (Fig. 6). Presumably, it was moved out by ciliary action and swallowed with the sputum. The large fraction remaining in the lungs was quite evenly distributed throughout the alveoli, and the pattern of distribution showed little change with time for intervals extending to two hundred and fifty-six days after the initial exposure. The slow and continued release of active material from the alveoli probably also took place primarily by way of the bronchial tree. This deduction is based on the observation that the fecal excretion of plutonium and the fission-product mixture closely corresponds to the elimination of these materials from the lungs.

The outstanding characteristic of 9 of the fission products described in this report, as well as neptunium and plutonium, to be accumulated and tenaciously retained by the skeleton has a most ominous significance. Justification for this opinion is borne out by the tragic situation that has surrounded the radium industry. There is evidence that the prolonged retention of 1 microgm. of radium may result in the appearance of bone tumors with a fatal outcome. Somewhat larger quantities of radium, in the range of 10 microgm. deposited in the skeleton, are frequently associated with aplastic anemia and occasionally leukemia. These conditions are presumably the result of the prolonged bombardment of the very radiosensitive bone marrow and the bone itself by the radiations arising from the radium deposited within the skeleton. The gloomy picture of radium poisoning is darkened further by the fact that, to date, no successful method has been developed for removing significant quantities of radium from the body once it has been locked in the mineral structure of the bone.

The fission products that localize in the skeleton are similar to radium in that they also tend to be tenaciously held in that organ, and, to date, no satisfactory procedure for removing these substances from the bone has been developed.[14, 15] A number of considerations reduce the relative menace of these fission products and neptunium^{239} as radioactive poisons in comparison to radium. In the first place they give up much less energy per disintegration, and the density of ionization is relatively much less since they emit only beta and gamma rays. Moreover, on the basis of an equal amount of ionization per unit volume of tissue, alpha particles are biologically considerably more destructive than beta and gamma irradiation. Secondly, with the exception of strontium^{90} and 61^{147} the more abundant fission products that are accumulated in the skeleton possess half lives of less than a year, whereas the half life of radium is approximately sixteen hundred years. Most of these fission products have half lives in the range of two weeks to two months. Thirdly, with the exception of strontium and barium, a negligible degree of absorption of these fission products and neptunium takes place through the digestive tract. However, with this group of radioelements there is one consideration that tends in part to counterbalance the considerations listed above, and that is the property possessed by a number of them to concentrate themselves in the immediate vicinity

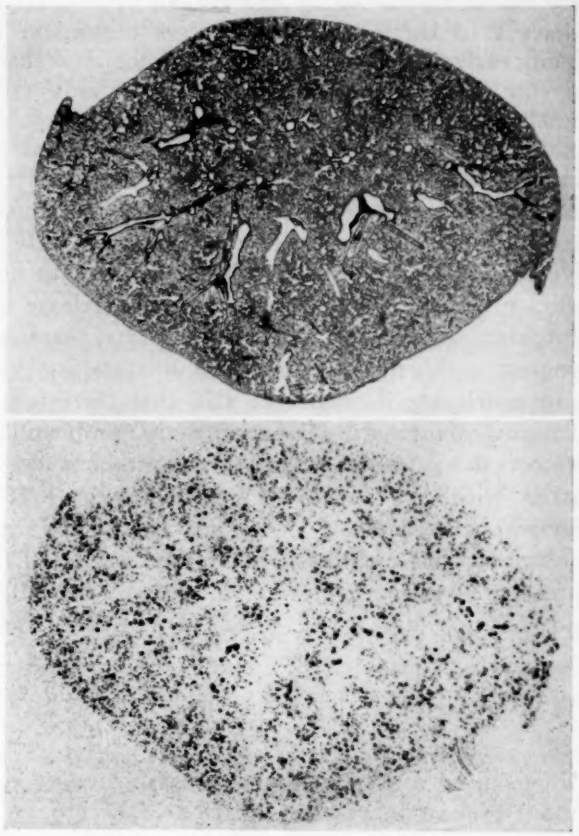

FIGURE 6. *Section of the Lung (Upper Photograph) and Corresponding Radioautograph (Lower) from a Rat Killed One Day after Inhalation of an Aerosol of Plutonium Oxide. The plutonium has disappeared from the bronchial surfaces, but it is widely distributed throughout the alveolar structures (hematoxylin and eosin stain x 4).*

of the bone marrow as contrasted to the more diffuse distribution of radium throughout the mineral structure of the skeleton. This behavior tends to enhance their radiotoxicity on the basis of both geometrical considerations and a minimal amount of self-absorption of the beta radiations, which are quite soft for several of the fission products under discussion. Plutonium shares the dangerous characteristics of radium — namely, a long half life (22,400 years), the emission of alpha particles, and the selective deposition and prolonged retention by the skeleton. In addition, the property of accumulating in the regions immediately adjacent to the bone marrow gives plutonium a significantly greater degree of radiotoxicity than an equivalent amount of radium. The only two metabolic properties of plutonium that tend to reduce this hazardous quality are the facts that it is absorbed to a negligible degree from the digestive tract and, presumably, that it is absorbed much less readily from the lungs than radium. Extensive studies have been made in an attempt to develop procedures that might effect the release of plutonium deposited in the bone. To date, practical progress in this direction has been discouraging.[14, 15]

In conclusion it should be said that there is no new major mystery surrounding the problem of protection against the radioactive products associated with the release of atomic energy. The physical phenomenon of radioactivity and its biologic actions have been known and subjected to intensive investigation for half a century. Recently, consideration has to be given to a much larger quantity of radioactivity arising from a somewhat greater number of radioactive elements than those which normally occur in nature. Although some of the problems presented by this new situation are formidable, to say the least, in retrospect many other formidable problems have been successfully passed by those working in the medical and related biologic sciences.

References

1. Nuclei formed in fission: decay characteristics, fission yields, and chain relationship. Prepared by J. M. Siegel. *J. Am. Chem. Soc.* **68**:2411-2442, 1946.
2. Smyth, H. D. *Atomic Energy for Military Purposes: The official report on the development of the atomic bomb under the auspices of the United States Government, 1940–1945.* 264 pp. Princeton: Princeton University Press, 1945.
3. Hamilton, J. G. Plutonium project: metabolism of fission products and heaviest elements. *Radiology* **49**:325-343, 1947.
4. Scott, K. G., et al. *Plutonium Project Record of the National Nuclear Energy Series*, MDDC-1275.
5. Scott, K. G., Axelrod, D. J., and Hamilton, J. G. Metabolism of curium in rat. *J. Biol. Chem.* **177**:325-335, 1949.
6. Carritt, J., et al. Distribution and excretion of plutonium administered intravenously to rat. *J. Biol. Chem.* **171**:273-283, 1947.
7. Hamilton, J. G. Use of radioactive tracers in biology and medicine. *Radiology* **39**:541-572, 1942.
8. Pecher, C. Biological investigations with radioactive calcium and strontium: preliminary report on use of radioactive strontium in treatment of metastatic bone cancer. *Univ. California Publ., Pharmacol.* (no. 11) **2**: 117-149, 1942.
9. Treadwell, A. deG., Low-Beer, B. V. A., Friedell, H. L., and Lawrence, J. H. Metabolic studies on neoplasm of bone with aid of radioactive strontium. *Am. J. M. Sc.* **204**:521-530, 1942.
10. Axelrod, D. J. Improved method for cutting undecalcified bone sections and its application to radiology. *Anat. Rec.* **98**:19, 1947.
11. Axelrod, D. J., and Hamilton, J. G. Radioautographic technique. *U. S. Nav. M. Bull.* **48** (Supp.): 122-141, 1948.
12. Scott, K. G., Axelrod, D. J., Crowley, J., Lanz, H., and Hamilton, J. G. Studies on inhalation of fissionable materials and fission products and their subsequent fate in rats and man. *Plutonium Project Record of the National Nuclear Energy Series*, MDDC-1276.
13. Scott, K. G., Axelrod, D. J., and Hamilton, J. G. Deposition and fate of aerosols of plutonium, uranium, and their fission products in the lungs of rats and man. *Arch. Path.* (in press).
14. Copp, D. H., Axelrod, D. J., and Hamilton, J. G. Deposition of radioactive metals in bone as potential health hazard. *Am. J. Roentgenol.* **48**:10-16, 1947.
15. Van Middlesworth, L. *The Study of Plutonium Metabolism in Bone.* 97 pp. University of California (Berkeley) Ph.D. thesis, 1947.

THE RADIATION SYNDROME*

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IN EARLIER studies of radiation effects in mammals, dosages of 1000 r and above have generally been employed locally or over large areas of the body. Actually, when irradiation is given as a single total-body dosage, the quantity necessary to kill 50 per cent of the animals in thirty days or less is relatively small: 175 to 250 r for the guinea pig, 325 r for the dog, 350 r for the goat, 530 r for mice, 600 r for rats, and 800 r for rabbits.[1,2] Where the LD_{50} for man lies is questionable, but it is probably somewhere between those for the goat and the mouse.[3]

Since Hiroshima, various writers[4-7] have reported the effects of very high instantaneous dosages of radiation. The fact that the victims of the atomic bombing showed a more complicated picture than the radiation syndrome alone is due not only to the blast effects but also to thermal effects that produced severe, superficial flash burns in a large proportion of the affected population. The ultraviolet light given off at the moment of detonation may also have been a factor.[8] In other respects the persons exposed to radiation from the atomic bomb appear to have shown a clinical picture extraordinarily similar to that which has been seen in laboratory animals.

In the 1920's the work of Warren and Whipple[9] and of Ivy et al.[10] contributed much to knowledge of the gastrointestinal changes following radiation. Their work indicated that these changes may be responsible for the conditions leading to early death as well as changes of the blood-forming organs. Much of the literature on the effects of radiation upon the stomach and the intestines has been reviewed by Desjardins.[11] During this period studies on a variety of physiologic systems were presented by Swann.[12] Thorough blood studies were made on animals by Levin[13] and on man by Lapatsanis.[14]

In the next decade the work of many investigators in the field of radiation centered on the measurement and standardization of dosage, on the question of "tolerance" and on the treatment of radiation sickness in man during and after x-ray therapy. Radiation sickness was compared with all types of shock and was treated in like manner. Much of the work was qualitative and not conclusive. Reviews by Pohle,[15] by Steinberg[16] and by Medinger and Craver[17] are helpful in their coverage of the literature, but are somewhat discouraging so far as the solution of the problem is concerned. For radiation therapy, they suggest dividing the doses or giving continuous radiation for a long time at a very low rate (0.8 to 0.9 r per hour) to prevent the occurrence of the initial phase of radiation sickness. It appears that of the drugs studied, sodium chloride, benzedrine (amphetamine), benadryl and epinephrine[16, 18-20] are of some therapeutic value, whereas liver extract, components of the vitamin B complex and vitamin C, and pentose nucleotides are not clearly restorative. Vitamin C, pentose nucleotides and nicotinamide will lengthen the survival time for mice when they are given for several days prior to exposure to x-rays. They will have little or no effect on survival time when given after irradiation.[6] Estrogenic hormones also appear to exert a protective effect when given several days before irradiation.[21] Steinberg[16] and others believe that further investigations should be made on the adrenal cortex and its possible alterations to throw light upon the development of more adequate therapeutic measures. Recently, Ellinger[22] has attempted to establish a pharmacologic basis for use of substances in the treatment of radiation damage. He has found that the mortality in mice can be reduced by daily doses of desoxycorticosterone and that the fat index (accumulation of sudanophil fat) in mice can be reduced by daily doses of components of the vitamin B complex and vitamin C. The effectiveness of adrenocortical material has not been verified universally.[21]

Early in the 1940's Warren and his co-workers[23] presented a thorough review of the pathology associated with radiation damage of normal tissues. Later, Warren briefly reviewed some specific biologic changes following radiation. It is the purpose of this paper to summarize the theoretical aspects of the biologic action of ionizing rays upon the organism and to outline the clinical manifestations of the radiation syndrome. The references selected for the following discussion represent both a review of the literature and experimental data gathered during the past five years.

THEORETICAL ASPECTS

Crowther,[25] in an analysis of studies of other investigators using simple systems such as single cells and unicellular organisms, proposes that the biologic action of radiation is specific upon the nucleus, in that this structure in the resting stage is twenty-five times as sensitive as the cytoplasm of the cell. Two contrasting theories are proposed. The one that he calls the "poison" theory postulates

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that, by means of photochemical action on the substance of the nucleus, a certain amount of some unspecified poisonous material accumulates and diffuses to the outlying structures, which then manifest the changes observed. The second or "target" theory assumes the occurrence of a change wherever a pair of ions is produced within the sensitive structure and enables calculation of this "sensitive volume." Since genes are hit so readily, Crowther believes that the strong genetic effect is consistent with the discontinuous distribution of the x-ray energy being absorbed. He favors the second theory and is supported in his contention by Reboul[26] in his mathematical presentation of the biologic effects of radiation. The target theory is discussed in detail by Lea[27] as a likely explanation for gene mutations or chromosome breakage following the passage of an ionizing particle through such structures.

Zirkle[28] points out that the variations in relative biologic effectiveness of different types of radiation can be explained by differences in specific ionization of these rays in the tissue. To determine the specific ionization, the average ionization per unit length of alpha or beta tracks in the tissue must be calculated, the unit of expression being the number of ion pairs produced per centimeter of the ionizing track in tissue. This increases progressively from fast beta rays to gamma rays, and then to hard and soft x-rays, fast neutrons and alpha rays — that is, the alpha rays have the greatest specific ionization. By the term relative biologic effectiveness, Zirkle implies the use of some definite criteria for determining the effectiveness, such as gene mutations, inhibition of cell division and threshold erythema.

When comparisons of two or more types of ionizing radiations are made upon simple systems, viruses, bacteria, drosophila, chick fibroblasts and so forth, Zirkle finds that the biologic effectiveness decreases as the specific ionization increases. For more complicated systems, like the higher phyla of plants (seedlings of flowers and vegetables) and of animals (mouse, rabbit, pig and man), biologic effectiveness increases, in general, as the specific ionization increases.

Another hypothesis is that of Failla,[29] whose thesis is illustrated by the experimental work of Sugiura.[30, 31] The latter was interested in the mechanism of the radiosensitivity of mouse sarcoma 180 cells and the part played by the host tissue in their "takes," since it has been generally assumed that the lethal dosage of x-rays for tumors growing in animals is much smaller than the dosage required to kill the same tumors in vitro. He found that there is a critical period for the host cells during the first two to forty-eight hours after radiation, at which time there is disorganization of these cells and, parallel with this, a decrease in the number of "takes" of tumor transplants. At six or seven days after radiation, however, the "takes" are 100 per cent successful. Further experimentation indicated a relation between these differences and hydration phenomena — that is, the ions produced by the radiation give rise to chemical changes in the constituents of the host cells with an alteration in their normal state and subsequent increase in their osmotic pressure. Ionizing radiation, therefore, initiates the swelling of cells. The swelling coupled with other changes caused by the radiation leads to cell death. The relation of chemical changes produced by radiation to the above phenomena requires much further explanation.

That chemical changes occur in aqueous systems as a result of ionizing radiation is now well understood.[32] The production of hydrogen peroxide and other oxidants in irradiated water is used by Barron[33] in explanation of the specific radiation sensitivity of certain enzymes (those having sulfhydryl groups) in contrast to the more radioresistant enzymes, which at the same time are less sensitive to oxidative inactivation. Fricke's[34] work on the reduction of oxygen to hydrogen peroxide by irradiation of its aqueous solution was the introduction to this concept. The oxidation theory of chemical alteration is supported by workers whose investigations show that there is an increased resistance to the action of x-rays when the blood flow through an area being irradiated is reduced,[35] or when animals are partially dehydrated before exposure to radiation.[2]

In his recent book, Lea[27] summarizes all the possible modes of biologic action of radiations. His main thesis is that the biologic effects are due to chemical changes induced by radiation. The greater part of these changes is attributed to the direct action of radiation with production of ionization in particular molecules and the indirect action of ionized water inside and outside the cells. No doubt other molecular effects of radiation are concerned in radiation effects, but the changes in water are best understood and, because of the abundance of water in living matter, may be the most important.

The Radiation Syndrome

The clinical sequence of the radiation syndrome is dependent upon several factors. Obviously, it can be clearly defined only through constant observation of the same animal. It is dependent upon whether the total dosage is given homogeneously to the whole body or whether it is confined to certain parts of the body. Localization may be accomplished by intense homogeneous radiation of part of the body or by exposure to soft radiation (alpha or beta rays) that may be directed toward external surfaces of the body or through deposition of radioactive isotopes having the tendency to localize in certain tissues or cells. Thus, partial body radiation may involve either a segment of the body or a particular group of tissues.

Radiation may be given by single, intermittent or continuous treatment, and the dosage rate may be varied. These factors will influence the syndrome considerably.[16, 17]

Despite the complexity of the problem as indicated above, it is found that the general features of the clinical course are similar whether ionization in the tissue is produced by penetrating external radiation[20, 36-38] or by alpha or beta emitters from internally deposited radioactive materials.[2, 39] Slight variations in the clinical course are indicated by mortality waves and by coincidental clinical observations. It is interesting to note the correlation of the underlying changes occurring on a cellular level with such diverse forms of damage as beta-ray exposure to skin.[40] These separate and distinct time periods for gross pathophysiologic changes in skin were originally defined by Miescher[41] as occurring on or at the end of the first day, the first week and the first month after irradiation. Telangiectasis occurs at about one year. The mechanisms involved in the production of these three erythemas and of the telangiectasis have been elaborated on by Pohle,[42] Borak[43] and others.

If single supralethal dosages of total-body radiation are given to guinea pigs and mice, they will die under the beam with generalized cellular destruction.[44, 45] Dogs and rats will die in four to six days with severe dehydration.[9, 46]

At single total-body dosages equivalent to killing within thirty days of 50 per cent of the animals (325 r for dogs), the manifestations are somewhat different from those described above and are spaced over a sufficiently long period to allow for detailed physiologic studies. At such dosages, the gross clinical changes may be classified under four periods in the different species: initial shock or radiation sickness, beginning after a latent phase of one hour following the radiation and lasting sometimes as long as twenty-four hours; acute period lasting from nine to twenty-one days; subacute period lasting from thirty to two hundred days; and chronic period, from two hundred days on. Careful study of the syndrome will indicate additional phases within the above. Manifestations differ in various species, but the general pattern is seen in all.

Initial Shock (Radiation Sickness)

After an LD_{50} of external radiation, there occurs a latent period of one to two hours in the different species, during which no significant physiologic changes are observed. The dog, rat, mouse, guinea pig, goat and man show signs of radiation sickness during the first six hours. This condition is characterized by prostration, diarrhea, urination, lacrimation and decreased food and water consumption. Some rabbits as well as chickens will die at three to forty-eight hours. In addition, rabbits show granulocytosis during the first twenty-four hours and a marked fall in blood pressure, approximately 50 to 60 per cent below the control levels one or two hours after irradiation. The change in pressure is due in part to autonomic factors as shown by partial protection with atropine or by vagotomy and in part to circulating factors as shown by transfusion experiments. Control studies on normal recipients from which half the blood volume had been removed and gradually replaced with the same quantity of blood from normal donors showed a 5-mm. change in blood pressure, whereas normal recipients transfused in a similar manner with blood from irradiated donors showed a 26.5-mm. drop in pressure. These circulatory changes are accompanied by leakage of plasma and its constituents from cutaneous vessels, observed as diffusion of the blue dye, T-1824, and of fluorescein.[20, 47]

In man and in the dog, nausea, vomiting and anorexia occur during this early period, but there appears to be no significant change in blood pressure. For the most part, changes in blood chemistry in all species examined are slight.

The extent to which early treatment of radiation sickness alleviates or delays the clinical symptoms that occur at nine to twenty-one days (acute period) has not yet been determined.

Acute Period

This is the period when most of the animals given a thirty-day LD_{50} of external radiation die. Generally, animals show recovery from the initial lethargic state a few hours after irradiation and remain in apparently good clinical condition until the seventh or eighth day. The depression that follows may be either gradual or abrupt and may occur at any time in the next few days. Before clinically visible changes appear, however, there are alterations in many physiologic systems. The most sensitive systems — that is, those showing the earliest changes with the lowest dosages of radiation — are the blood-forming organs, the gastrointestinal tract and the gonads. The absolute lymphocyte count declines abruptly, whereas the count of granulocytes declines more gradually (after the initial granulocytosis in rabbits). Diminution in number of circulating lymphocytes is the most sensitive evidence of exposure yet found. Evidence of the changes in other systems is manifested on the third or fourth day by increased sedimentation rate of the blood cells and prolonged clotting time. On the sixth to the tenth day, there is an increased plasma clearance of phenol red (with return to normal about the twelfth to the fourteenth day), an increase in the plasma volume as the red-cell volume decreases, rise in blood sugar, later followed by a fall, increase in plasma histamine, heparin, cholesterol and acetone bodies, diminution of plasma nonprotein nitrogen, urea nitrogen, "polypeptide nitrogen" and total proteins followed by a late increase, decrease in fecal and urinary coproporphyrins, elevated urobilinogen and bilirubin, lowering

of gastric acidity, reduced absorption of glucose by the intestine and delayed emptying of the intestine, and ulcers begin to appear in mouths of dogs.[1] The relation of these numerous findings to the underlying physiologic and structural changes and to compensatory processes is not in all cases clear.

The late (or terminal) changes occur precipitously three or four days before death, and some of them may appear briefly in survivors before a gradual recovery sets in. These include scattered petechiae and diffuse hemorrhages in the skin, a marked rise in heart rate, a gradual fall in blood pressure, an increase in body temperature and, in some animals, edema of the neck and mediastinal regions. The cardiovascular damage has been observed most frequently in the dog. Changes in the heart are indicated by the change in the electrocardiogram, which shows a slight increase in the PR interval, a low take-off and an inverted T wave in Leads 1 and 2. This has been most obvious in animals that, on autopsy, showed extensive hemorrhages in the cardiac muscle. Changes in the peripheral circulation are apparent in many ways: there is difficulty in drawing blood from small vessels; clumping of red cells with loss of plasma from vessels can be observed microscopically; and slight trauma to skin results in ecchymosis or edema. On autopsy, widespread hemorrhages and petechiae are found throughout all the tissues, including the central nervous system and the kidneys.

A highly significant factor in the bleeding tendency has been described by Allen and Jacobson,[48] who observed that a greatly increased heparin concentration ran parallel to the prolonged clotting time. The progressive hemorrhages were stopped and the clotting time was returned to normal by the administration of toluidine blue or protamine, both of which inactivate the heparin.

TABLE 1. *Effects of Threshold Dosages of Total-Body X-Rays.*

Dosage r	Effect
25	Lymphopenia (dogs, rabbits, rats)
50	Granulocytopenia (dogs)
	Reduction in platelet count (dogs)
	Reduction in blood pressure (rabbits)
	Elevation of basal metabolism (rats)[49]
	Inhibition of intestinal absorption of glucose (rats)
100	Granulocytopenia (rabbits)
	Elevation of sedimentation rate (dogs)
	Anemia (dogs, rabbits)
200	Absence of reticulocytes (dogs)
	Prolongation of clotting time (dogs)

In this later period there is also evidence of liver dysfunction as shown by the changes in bile-pigment metabolism. Plasma nonprotein nitrogen and urea nitrogen show a marked rise, associated with the increase in body temperature, with the decreased kidney function and with an increase in total tissue breakdown. The latter has been determined by direct and indirect metabolic measurements. At this stage the picture is typical of a general toxemic reaction. Toxins may be expected in the presence of bacterial infections occurring with the extreme leukopenia and may also come from the products of tissue breakdown or of extravasated blood.

It may be of interest to mention threshold dosages of total-body x-ray that will just produce certain of the physiologic effects discussed above. These are approximately as shown in Table 1, according to Prosser.[49]

Subacute Period

Animals surviving a single LD_{50} of radiation for thirty days or longer fall into this category. Dogs receiving daily x-ray dosages of 25 r or below or low dosages of the internal emitters, plutonium or strontium[89] (radium in man[51]) will die between thirty and two hundred days.

The characteristic changes during this period are severe anemia, emaciation, loss of hair and pigmentation of the skin; terminally, ulcers are found in the duodenum and jejunum of dogs. The animals that receive the internal emitters or daily dosages of x-rays do not show the early shock-like symptoms, but they may show from two to four depression waves between the original injection, or the first exposure to radiation, and death. These waves are manifested by reduction in the red-cell count, by general lethargy and by decreased food and water intake. Hematologic changes develop very gradually and show fluctuations with the depression waves, as do the changes in other physiologic systems. Several days prior to death there occurs an increase in heart rate and an increase in body temperature similar to the changes observed in dogs in the terminal phase of the acute period.

Chronic Period

In animals receiving still lower dosages of x, alpha or gamma rays, decreased life-span, graying of dark-haired animals and the development of tumors constitute the chronic changes after irradiation. In mice, lymphomas, lymphatic leukemia and lung tumors are readily induced by total-body irradiation. Many species develop tumors of certain tissues after local irradiation by alpha-emitting or beta-emitting substances. Especially noteworthy are the multiple skin tumors resulting from external beta irradiation and bone tumors following absorption of radium, strontium[89], plutonium and other radioactive isotopes.[52] In addition to high incidences of malignant tumors in areas receiving relatively heavy dosages of radiation, the normal tumor incidence in various species of animals is increased (or tumor development is accelerated) after either a single high dose or repeated or continuous exposure at a low level.[53] The degree of enhancement of the normal tumor incidence ap-

pears proportional to the amount of absorbed radiation, although its occurrence at low radiation levels (below 0.5 to 1 r daily) has not been clearly demonstrated, owing to the experimental difficulty of showing the low incidences that might be expected. Whether a threshold exists for carcinogenesis or effects on longevity is therefore unknown.

A noteworthy feature of the carcinogenic effect of radiations is the duration of the latent period, which, even under the most intense local stimulation, is rarely less than six months. It appears that radiation carcinogenesis is little dependent on species, in contrast to chemical carcinogenesis, in which the metabolism of the carcinogen may be a factor.

Therapy

As mentioned above, adequate methods of treatment for radiation damage are lacking. The main objectives in the management of patients are to maintain adequate fluid and acid-base balance, to control infectious processes, to combat the hemorrhagic phenomena and to correct anemia and blood-volume changes.

Investigations have been most successful along the lines of increasing survival time, and of reducing the bleeding tendency. In the latter case, protamine and toluidine blue offer some promise. Penicillin and other antibiotics appear indicated for the control of infection. It appears, in general, that other forms of therapy are as yet not established (for example, adrenocortical material and rutin), must be given prior to irradiation or (as in several adjuvants mentioned above) apply only to the initial reaction as seen during the day following x-ray therapy.

Discussion

No single clinical reaction is peculiarly specific for radiation damage. A similar preterminal course with leukopenia and high sensitivity of dividing cells is found with such agents as the nitrogen mustards[54] and urethane[55]; the acute terminal course with fever and petechiae is characteristic of acute infections and of many diseases. There are striking similarities to anaphylactic shock and to the nonspecific (alarm) reactions to a variety of diverse toxic agents given in sublethal amounts,[56] and to the agranulocytic states accompanying drug sensitization. Many of the delayed effects of radiation can be duplicated by various toxic chemicals, such as anemia and leukemia in benzol poisoning, or tumor induction by hydrocarbons or ultraviolet light.

The relation between the initial physical and chemical effects of radiation remains largely to be worked out. It seems reasonable to believe that the primary effects all occur during radiation and for a brief period thereafter, since the lifetime of the chemical products of ionization in water is short.

With the exception of the initial reaction, the acute phenomenon of the radiation syndrome follows a latent period during which cell damage and atrophy of the more sensitive tissues occur. Since these tissues (blood-forming organs, intestine and gonads) are proliferative, it is tempting to suggest that damage to chromosomes (which is known to lead to cell death at a subsequent cell division) accounts for the damage. The picture may well be more complicated than this. In any case, many of the features of the radiation syndrome can be accounted for by destruction of the sensitive cell types. There is some evidence that agranulocytosis, rather than lymphopenia, correlates with the lethal dose among the various species of animals.[57] Many of the early changes in the syndrome, such as increased renal blood flow and elevated sedimentation rate, suggest the presence of circulating toxins, whereas many of the late changes appear to be associated with hemorrhage due to the release of heparinoid material into the blood, probably from injured cells.

The nature of toxic materials that may be involved in the shock-like state is far from clear. It will be recalled that in certain forms of traumatic shock in which such toxins are present, bacteria have been clearly shown to be responsible.[58]

The events leading to the chronic phenomena are still less well understood. The fact that radiation induces genetic changes has suggested that carcinogenesis is due to similar changes in somatic cells resulting in mutant cells that have the characteristics of neoplasia, but various other explanations may be entertained. The shortening of life span has been loosely termed "increased aging," but evidence for this involves all too meager understanding of the aging process, and will await study of the various pathologic states that lead to shortening of life, among which tumor formation is probably only one.

Summary

The radiation syndrome, produced by a single total-body thirty-day LD_{50} of external radiation or of internal emitters of alpha or gamma rays, is characterized by three separate and distinct periods: the initial shock reaction or radiation sickness, the acute and the subacute. The initial shock may last from three to forty-eight hours. Occasionally rabbits and chickens die during the initial period. Other animals, such as dogs, rats, guinea pigs and goats, do not die, but show prostration, diarrhea, urination, lacrimation and decreased food and water consumption. In addition, man and the dog often vomit.

The acute period lasts from nine to twenty-one days, during which most of the animals die. The preterminal changes and the sharp delineation of the terminal signs are discussed in detail. Some of the radiation effects are directly due to destruc-

tion of certain tissue elements. Many others are indirect and may be attributed to infections, toxic agents, hypoxia and other secondary factors.

Animals surviving thirty days or more fall into the subacute category, where fluctuations of recovery and depression of the leukocytes do not permit the use of the white-cell count for determining the progressive changes of radiation damage. A severe anemia, emaciation and graying of dark-haired animals are the usual signs of the radiation syndrome in this phase. The chronic phase is characterized by shortening of life and sporadic increase in tumors.

Nearly every physiologic system shows damage after total-body irradiation. The effects are nonspecific. Many of the same manifestations are shown in the animal organism by the administration of the nitrogen mustards or urethane, in anaphylactic shock, agranulocytosis, the "alarm reaction" of Selye and benzol poisoning. Damage to the radiosensitive cells will explain a great part of the picture, but much further understanding of the syndrome is required in the interest of prevention and therapy.

References

1. Prosser, C. L., et al. *The Clinical Sequence of Physiological Effects of Ionizing Radiation in Animals.* (Short Form.) MDDC-611.
2. Ellinger, F. Lethal dose studies with x-rays. *Radiology* **44**:125-142, 1945.
3. Warren, S. Histopathology of radiation lesions. *Physiol. Rev.* **24**:225-238, 1944.
4. Larkin, J. C. Distribution of radiation in atomic bombing of Nagasaki. *Am. J. Roentgenol.* **55**:525-532, 1946.
5. Keller, P. D. Clinical syndrome following exposure to atomic bomb explosions. *J. A. M. A.* **131**:504-506, 1946.
6. Warren, S. Pathologic effects of instantaneous dose of radiation. *Cancer Research* **6**:449-453, 1946.
7. Leroy, G. V. Medical sequelae of atomic bomb explosion. *J. A. M. A.* **134**:1143-1148, 1947.
8. Brues, A. M., Henshaw, P. S., Block, M. A., Neel, J. V., and Ullrich, F. W. *General Report of the Atomic Bomb Casualty Commission, Tsuzuki, M. Report on Medical Studies of the Effects of the Atomic Bomb.* Appendix No. 9. Pp. 67-111. National Research Council. Privately circulated. January, 1947.
9. Warren, S. L., and Whipple, G. H. Roentgen ray intoxication. *J. Exper. Med.* **35**:187-211, 1922.
10. Ivy, A. C., McCarthy, J. E., and Orndoff, B. H. Studies on effect of roentgen rays on glandular activity. IV. Effect of exposure of abdominal and thoracic areas to roentgen rays on gastric secretion; note on roentgen cachexia. *J. A. M. A.* **83**:1977-1984, 1924.
11. Desjardins, A. U. Action of roentgen rays and radium on gastrointestinal tract. *Am. J. Roentgenol* **26**:151-190 and 337-370, 1931.
12. Swann, M. B. R. Study of immediate effects of x rays on functions of certain tissues and organs. *Brit. J. Radiol.* **29**:195-220, 1924.
13. Levin, I. Action of radium and x-rays on blood and blood-forming organs. *Am. J. Roentgenol.* **9**:112-116, 1922.
14. Lapatsanis, P. Beitrag Zur Allgemeinwirkung der Röntgenstrahlen auf den menschlichen Organismus. *Strahlentherapie* **22**:484-502, 1926.
15. Pohle, E. A. Principles of roentgentherapy. *Wisconsin M. J.* **29**:149-153 and 207-212, 1930.
16. Steinberg, S. S. Irradiation sickness: critical study. *Am. J. Roentgenol.* **47**:56-65, 1942.
17. Medinger, F. G., and Craver, L. F. Total body irradiation, with review of cases. *Am J. Roentgenol.* **48**:651-671, 1942.
18. Jenkinson, E. L., and Brown, W H. Irradiation sickness: hypothesis concerning basic mechanism and study of therapeutic effect of amphetamine and dextro-desoxyephedrine. *Am. J. Roentgenol.* **51**:496-503, 1944.
19. Lofstrom, J. E., and Nurnberger, C. E. Irradiation sickness: histamine effect treated with benadryl: preliminary report. *Am. J. Roentgenol.* **56**:211-219, 1946.
20. Painter, E. E., Prosser, C. L., and Moore, M. C. *Physiological Observations on Rabbits Exposed to Single Doses of X-rays.* MDDC-761.
21. Patt, H. M., Swift, M. N., Clayton, R., Tyree, E. B., and Straube, R. L. *Quarterly Report, Biology Division, Argonne National Laboratory.* May, 1948, ANL-4163.
22. Ellinger, F. Influence of pharmacological agents of effects of irradiation. *Radiology* **50**:234-243, 1948.
23. Warren, S. Effects of radiation on normal tissues. *Arch. Path.* **34**: 443-450, 562-608, 749-787, 917-931, and 1070-1084, 1942. **35**:121-139 and 304-353, 1943.
24. *Idem.* Physiological effects of radiant energy. *Ann. Rev. Physiol.* **7**:61-74, 1945.
25. Crowther, J. A. Biological action of x rays — theoretical review. *Brit. J. Radiol.* **11**:132-145, 1938.
26. Reboul, J. Théorie générale de l'action des rayons X sur les éléments biologiques. *Compt. rend. Acad. d. sc.* **208**:229-231, 1939.
27. Lea, D. E. *Actions of Radiations on Living Cells.* 402 pp. New York: Macmillan Co., 1947.
28. Zirkle, R. E. *Radiobiological Importance of Specific Ionization.* MDDC-444.
29. Failla, G. Some aspects of biological action of ionizing radiations. *Am. J. Roentgenol.* **44**:649-664, 1940.
30. Sugiura, K. Studies on radiosensitivity of mouse sarcoma 180 irradiated in vivo and in vitro. *Radiology* **29**:352-361, 1937.
31. *Idem.* Effect of injections of distilled water on growth of irradiated mouse sarcoma 180. *Am. J. Roentgenol.* **43**:533-538, 1940.
32. Burton, M. Radiation chemistry. *J. Physical & Colloid Chem.* **51**: 611-625, 1947.
33. Barron, E. S. G., Singer, T. P., Muntz, J. A., Gasvoda, B., and Hopkins, J. M. *Some Aspects of the Biological Action of Radiation.* MDDC-484.
34. Fricke, H. Reduction of O_2 to H_2O_2 by irradiation of its aqueous solution with x rays. *J. Chem. Physiol.* **2**:556, 1934.
35. Evans, T. C., Goodrich, J. P., and Slaughter, J. C. Temperature and radiosensitivity of skin of newborn rats. IV. Effects of decreased circulation and breathing during irradiation. *Radiology* **38**:201-206, 1942.
36. Ducuing, J., Miletzky, O., and Marques, P. Recherches expérimentales sur les modifications sanguines provoquées par des irradiations totales à l'aide des rayons X. *Sang* **11**:483-504, 1947.
37. T'ang, Y. Les bases expérimentales de la radiothérapie totale et subtotale. *J. belge de radiol.* **28**:207-299, 1939.
38. McDonald, E., et al. *Neutron Effects on Animals.* 198 pp. Baltimore: Williams & Wilkins Co., 1947.
39. Lacassagne, A., Lattès, J., and Lavedan, J. Étude expérimentale des effets biologiques du polonium introduit dans l'organisme. *J. d. radiol. et d'électrol.* **9**:1-14 and 67-82, 1925.
40. Robbins, L. L., et al. Superficial "burns" of skin and eyes from scattered cathode rays. *Radiology* **46**:1-23, 1946.
41. Miescher, G. Das Röntgenerythem. *Strahlentherapie* **16**:333-371, 1924.
42. Pohle, E. A. Studies of roentgen erythema of human skin: skin capillary changes after exposure to unfiltered radiation. *Radiology* **6**:236-245, 1926.
43. Borak, J. Radiation effects on blood vessels: erythema: edema. *Radiology* **38**:481-492, 1942. 'Radiation effects in blood vessels: inflammation: degeneration: suppression of growth capacity: retrogression. *Ibid.* **38**:607-617, 1942. Radiation effects on blood vessels: telangiectasis: effects on lymph vessels. *Ibid.* **38**:718-727, 1942.
44. Henshaw, P. S. Experimental roentgen injury. III. Tissue and cellular changes brought about with single massive doses of radiation. *J. Nat. Cancer Inst.* **4**:503-512, 1944.
45. Henshaw, P. S., and Curtis, H. J. Unpublished data.
46. Moon, V. H., Kornblum, K., and Morgan, D. R. Nature and pathology of radiation sickness. *J. A. M. A.* **116**:489-493, 1941.
47. Rigdon, R. H., and Curl, H. Effect of roentgen irradiation on capillary permeability and inflammation in skin of rabbit. *Am. J. Roentgenol.* **49**:250-257, 1943.
48. Allen, J. G., and Jacobson, L. O. Hyperheparinemia: cause of hemorrhagic syndrome associated with total body exposure to ionizing radiation. *Science* **105**:388, 1947.
49. Prosser, C. L. Clinical sequence of physiological effects of ionizing radiation in animals. *Radiology* **49**:299-313, 1947.
50. *Idem.* Unpublished data.
51. Martland, H. S. Occurrence of malignancy in radioactive persons: general review of data gathered in study of radium dial painters, with special reference to osteogenic sarcoma and interrelationship of certain blood diseases. *Am. J. Cancer* **15**:2435-2516, 1931.
52. Brues, A. M., Lisco, H., and Finkel, M. *Carcinogenic Action of Some Substances Which May Be a Problem in Certain Future Industries.* MDDC-145.
53. Lorenz, E. *Biologic Effect of Long-Continued Whole-Body Irradiation with Gamma Rays on Mice, Guinea Pigs, and Rabbits.* Part VI. *Conclusions and Applicability of Results to the Problem of Human Protection.* CH-3697.
54. Gilman, A., and F. S. Philips. Biological action and therapeutic applications of β-choroethyl amines and sulfides. *Science* **103**:409-415, 1946.
55. Paterson, E., Haddow, A., Thomas, I. A. and Watkinson, J. M. Leukaemia treated with urethane compared with deep x-ray therapy. *Lancet* **1**:677-682, 1946.
56. Selye, H. Studies on adaptation. *Endocrinology* **21**:169-188, 1937.
57. Brues, A. M., and Rietz, L. *Quarterly Report, Biology Division, Argonne National Laboratory.* November, 1948, ANL-4227.
58. Aub, J. C., et al. Bacteria and "toxic factor" in shock. *War Med.* **5**:71-73, 1944.

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VARICOCELE*

Symptomatologic and Surgical Concepts

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IN RECENT years the treatment of symptomatic varicocele has become a subject of renewed endeavor. The interest was stimulated by the degree of disability this condition caused among members of the armed forces during World War II. Low scrotal-vein ligation, the operation in vogue prior to 1942, had fallen into disrepute because of persistence of symptoms and the frequency of surgical complications. For these reasons a new operative technic, which had been popularized in Latin America, was tried by Army surgeons.[1, 2] Reported series of cases[1-4] in which this operation was performed and evaluated showed the procedure to be surprisingly effective.

In civilian life the discomfort and disability associated with varicocele continue to interfere with the efficiency of thousands of workers. In an attempt to relieve those who sought relief at this hospital, this newer technic of high ligation of the internal spermatic vein was adopted. This paper presents a critique of the varicocele syndrome and the results obtained in 25 cases.

PATHOLOGICAL PHYSIOLOGY

The venous drainage of the scrotal contents can be compared to that of the extremities. Both deep and superficial systems are present. This concept of dual drainage was first expounded by Ivanissevich[5] in 1918, and is shown diagrammatically in Figure 1. His studies demonstrated a primary or deep system consisting of the internal spermatic vein, the ductus deferens vein, and the external spermatic vein. The latter two anastomose with the internal spermatic veins at the level of the external inguinal ring. The superficial or secondary drainage system was found to consist of the superficial and deep inferior epigastric veins, the superficial internal circumflex and the scrotal tributaries of the superficial and deep external and internal pudendal veins. These veins communicate freely with each other and with the primary system through the cremasteric branches of the external spermatic vein at the level of the external inguinal ring. The numerous convoluted veins of the pampiniform plexus coalesce as they course upward from the testicle until they become one large vein in the upper portion of the inguinal canal. This, the internal spermatic vein, then traverses the retroperitoneal space to empty on the left side into the renal vein at a 90° angle and, on the right, to empty obliquely into the vena cava. Study of the lengthy internal spermatic veins has

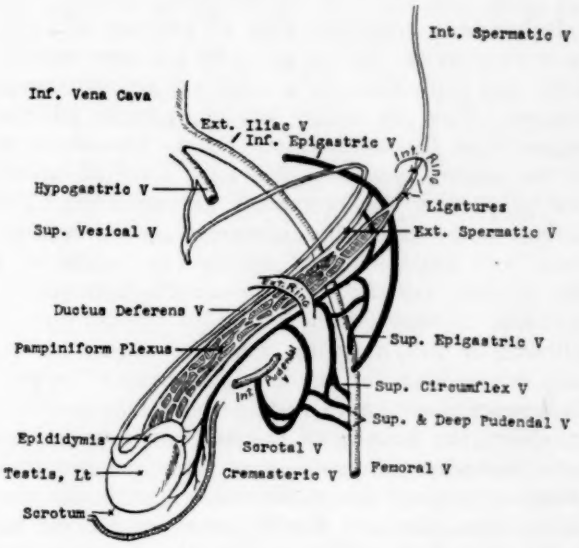

FIGURE 1. *Diagram of the Venous Drainage of the Scrotal Contents (Adapted from Javert and Clark[1]).*

Primary system — internal spermatic, ductus deferens and external spermatic veins (in white). Secondary system — superficial epigastric, superficial internal circumflex and cremasteric veins, and through scrotal tributaries the superficial and deep pudendal and the internal pudendal veins (in black).

shown them to be devoid of valves except at their point of emptying. Congenital and degenerative changes lead to valvular deficiency. It is this combination of a long vein and valvular incompetence that constitutes the etiology of varicocele. This results in a retrograde flow down the internal spermatic vein, causing overdistention of the pampiniform plexus in the upright position. The reverse venous flow can readily be shown at operation. If a distal segment of the internal spermatic vein is occluded and the vein stripped proximally between the fingers, immediate refilling of the stripped portion is noted on release of the proximal finger occlusion. The marked preponderance of left-sided varicocele can readily be appreciated as being due

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to the mechanical disadvantage in preventing backflow offered by the right-angled junction of the spermatic and renal veins as contrasted to the oblique entrance of the right spermatic vein into the vena cava. Further study of the venous anatomy makes obvious the fact that the point of anastomosis of the superficial and deep systems, at the external ring, is of crucial importance. It was disregard of this anatomic feature that caused the failure of the low ligation procedure. Venous interruption at the external ring leads to disruption of both systems of drainage, with a poorly draining scrotum. Utilization of the more recent conception of venous drainage led to the ligation of the internal spermatic vein, which is physiologic and therefore successful.

Clinical Picture

It has been estimated that 10 per cent of males have varicoceles. Of this group 98 per cent are left-sided and approximately a third are actively symptomatic. The age group most frequently affected ranges from fifteen to thirty years. Consideration of the altered venous physiology involved allows one to predict the symptoms of varicocele. The patient notes gradually increasing scrotal enlargement and pendulousness during the course of a day of erect posture. This process is hastened by exertion. A sense of heaviness of the scrotum is followed by dull, dragging, aching, constant, pulling pain felt in both the scrotum and groin. The pain disappears slowly with rest in the supine position. In short, the pain is of the traction type caused by a heavy scrotum pulling on the spermatic cord. Other symptoms are to be viewed with the suspicion that they are due to other pathologic entities. Sharp or stabbing pain should cause one to suspect the concomitant presence of orchalgia, epididymitis or hernia. Occasionally, local venous thrombosis secondary to trauma may give sharp localized pain in the scrotum for a short time. Some explanation must be offered for small symptomatic varicoceles in view of many large ones that do not cause discomfort. It is our opinion that all patients with varicocele can be found to have symptoms, if closely questioned. The pain threshold is so variable that some patients are bothered more than others. Such variability of response is seen in many diseases. Although an overlay of psychiatric disturbance undoubtedly adds to the patient's degree of response to his disease, we do not believe that it is necessary to ascribe such an implication to every patient with varicocele.

Physical examination should do much to clarify the picture. The "bag of worms," scrotal pendulousness and asymmetry and enlarged, soft spermatic cord are familiar to all. Painful testis or epididymis does not belong in the varicocele syndrome, and should lead to suspicion of other etiologic factors. Javert and Clark[1] have shown the presence of coexistent hernia in 25 per cent of their cases. The finding of hernia is much facilitated by examination in both the erect and the supine position. This allows more accurate evaluation of a possible hernial sac by fostering collapse of the distended vein while the patient is supine. In most cases, then, it should be possible to explain symptoms, whether severe or merely annoying, as due to varicocele, a coexistent varicocele and hernia or one of the ill defined syndromes of orchalgia or chronic epididymitis.

Treatment and Operative Technic

Although Ivanissevich[5] recommended retroperitoneal ligation of the internal spermatic vein as early as 1918 this method was not appreciated in the United States until Bernardi, in 1942,[4] reported his superior end-results from ligation at the internal inguinal ring. Present-day textbooks have as yet not assimilated the new literature and still offer a pessimistic outlook. Considerable emphasis is given to ascribing symptoms as due to overcongestion from unfulfilled sexual desires, scrotal fixation in psychoneurosis and other ill defined causative factors. Reassurance and the wearing of a suspensory are suggested as therapy. Surgery is considered unwise. The complications of the low ligation procedure — hemorrhage, painful thrombosis, testicular atrophy, epididymitis, hydrocele and recurrence — are admitted to be very frequent. The reason for this is now obvious. The procedure obstructs the venous drainage almost completely at the level where the anastomoses of the superficial and deep systems occur. It further fails to care for the gravity retrograde flow in the incompetent internal spermatic vein. The basic disorder is attacked at its source by the newer procedure, and the complications listed above are avoided. At the same time a concomitant hernia can be searched for. The region of anastomosis is spared. Adequate testicular suspension can be obtained.

The technic followed in this series varies only slightly from that described by Javert and Clark.[1] Through an oblique inguinal incision the external oblique fascia is split through the external ring to allow better exposure and a more effective herniorrhaphy. The spermatic cord is completely freed to the level of the internal ring. It is believed that this step allows for better eventual testicular suspension. The cremasteric fascia is opened longitudinally, and the internal spermatic vein isolated. Usually, one large vein, approximating a pencil in size, is found and is ligated at the internal ring, as is a secondary smaller vessel if present. In this series 15 patients had one vein, and 10 presented two veins, which in all cases were found to anastomose retroperitoneally. A 2-cm. to 5-cm. segment of the vein is excised, and the proximal end allowed to retract retroperitoneally. Careful search is then made for a hernial sac. If found, it is dissected free, and the sac ligated. It

is to be remembered that at this point forceful traction may pull down peritoneum and in so doing create a false sac that does not constitute a true hernia and does not need ligation.

Testicular suspension, which is next carried out, is considered very important for the final result. Three technics are followed: the distal vein stump is pulled proximally and sutured through the cremasteric fascia to the internal oblique muscle; the cremasteric fascia is closed transversely; and a further tightening of the lax spermatic cord is obtained by suture of the conjoined tendon under the cord to the shelving inguinal ligament. This lifts the cord by the mere presence of tissue beneath it. The external oblique is then resutured above the cord. Silk-suture material is used throughout the procedure. Postoperatively, the patient wears a suspensory for two weeks. He is allowed to be ambulatory on the first postoperative day and actually is eligible for discharge on or after the sixth postoperative day.

Evaluation of Cases

This series is small but does suggest certain trends in the varicocele syndrome. In 25 cases, the ages of the patients ranged from twenty to fifty-three years, and 20 were between twenty and thirty years old, which is in accord with the usually quoted figures of age frequency of symptoms. The duration of known scrotal enlargement showed a range of one to twenty years, with an average of four and two-fifths years. The duration of symptoms was much less, with a span of four months to five years and an average of two and a fifth years. Both enlargement and symptomatology showed a tendency to increase with time. Analysis of symptoms revealed that 21 of 25 patients had only the basic symptom complex of scrotal enlargement with dull, aching, dragging, scrotal and groin pain at the end of the day or after prolonged exertion. The pain was annoying as a rule, but in a few cases it was sufficiently distressing to require hours of bed rest for relief. The 4 atypical cases presented such variations as morning pain, sharp stabbing pain, localized scrotal pain, tender testes and intermittent attacks of pain. The effect of the type of symptoms on prognosis is discussed below.

On physical examination the varicocele was classified as large in 10 cases, moderate in 10, and small in 5. It was considered significant that 3 of 5 patients with small varicoceles had atypical symptoms. Only 1 patient was thought preoperatively to have a hernial sac. The incidence of hernia at operation was 12 per cent, with 3 small indirect sacs found. Moderately large lipomas of the spermatic cord were removed in 4 cases, and this proved to be the lesion present in the patient thought preoperatively to have a hernia.

The results have been grouped on a symptom basis to show the effect on prognosis of close evaluation of the symptom complex. A poor result was the case in which the patient continued to have scrotal pain even though it might vary in degree or type from the presenting complaint. In the typical symptom group of 21 cases, 20 were good results over periods ranging from three to twenty-four months. In the case regarded as a failure, twenty months after operation the varicocele was gone, but scrotal and epididymal pain in intermittent attacks persisted. Study of the patients with atypical symptoms revealed 3 out of 4 to have poor results. All had small varicoceles. Over a twenty-month follow-up period, 2 were symptomatically unchanged, and the third had intermittent attacks of pain. The varicoceles were gone. All originally presented elements of sharp scrotal pain in addition to testicular or epididymal tenderness. Under our present criteria they would not be considered as candidates for this procedure. Table 1 shows the breakdown of cases in terms of follow-up period and type of symptom. It is to be noted that we learned early the futility of operation in the atypical cases. The large percentage of good results among the patients with typical symptoms further emphasizes the importance of early, careful evaluation. In view of the marked emphasis placed on psychogenic factors in the literature, it is interesting to note that a group of 4 patients were being or had been treated for psychoneurosis. All presented symptoms that were considered typical of varicocele. The surgical results were excellent in 4 gratified patients. We were encouraged by this experience to believe that, in spite of known psychoneurosis, typical varicocele

Table 1. *Results according to Type of Symptoms.*

Follow-up Period	Patients with Typical Symptoms		Patients with Atypical Symptoms		Totals	
	Good Result	Poor Result	Good Result	Poor Result	Good Result	Poor Result
mo.						
3–6	6	0	—	—	6	0
6–12	2	0	—	—	2	0
12–18	9	0	—	—	9	0
18–24	3	1	1	3	4	4
Totals	20 (95%)	1 (5%)	1 (25%)	3 (75%)	21 (84%)	4 (16%)

syndrome with a physiologic basis can occur and can be helped by appropriate surgical operation.

The cosmetic results of high ligation have been completely satisfactory. All 25 cases showed a progressive shrinkage of the "bag of worms" from the day of operation to the completion of the process, usually within a month. Testicular suspension was very gratifying in that scrotal pendulousness was corrected as much as 4 or 5 cm. in some cases. All patients had scrotums that looked well within normal limits when the process of vein shrinkage, skin retraction and testicular suspension had reached its end point. Figure 2 and 3 show a typically good result.

FIGURE 2. *Preoperative Appearance, Showing the Engorged Pampiniform Plexus.*

This type of operative procedure was singularly free of complications. In 3 cases there were localized areas of slightly painful vein thrombosis, which disappeared within a month. No wound sepsis was present, and hematoma formation, testicular atrophy, hydrocele formation, epididymitis and scrotal induration were not noted.

SUMMARY AND CONCLUSIONS

The concept of dual drainage of the scrotal contents is reviewed.

A definite physiologic basis and type of symptom is postulated for the varicocele syndrome. It is stressed that symptoms not conforming to this pattern should suggest other disease as the source of the complaints.

The technic and rationale of operation are explained. A series of 25 cases showing 84 per cent good results is analyzed.

The opinion is stated and in part substantiated that the role of psychoneurosis in this condition has been overemphasized in the past.

The possible coexistence of hernia and varicocele is mentioned, and the facility with which both defects can be repaired in one operation explained.

The pessimistic attitude found in the literature regarding the results of surgery in the treatment of this condition does not seem warranted. On the basis of these results it appears fair to prognosticate that a patient with typical varicocele symptoms can be relieved of his scrotal distress and distortion by the high ligation technic with very little risk of operative complication. The operation seems contraindicated in atypical cases in which the varicocele is but an incidental part of another pathologic entity causing symptoms of its own.

FIGURE 3. *Postoperative Appearance. Note the lack of dilated veins.*

REFERENCES

1. Javert, C. T., and Clark, R. L. Combined operation for varicocele and inguinal hernia: preliminary report. *Surg., Gynec. & Obst.* **79**: 644-650, 1944.
2. Zucker, M. O. Newer concept of surgical treatment for varicocele. *Mil. Surgeon* **95**:515-517, 1944.
3. Riba, L. W. Excision of internal spermatic vein for varicocele. *J. Urol.* **57**:889-896, 1947.
4. Bernardi, R. Tratamiento quirúrgico del varicocele: conceptos y algunas modificaciones en su técnica. *Semana méd.* **2**:849-860, 1941.
5. Ivanissevich, O. O tratamento da varicocele. *Med. cir. pharm.* Pp. 646-662, September, 1942.

EOSINOPHILIA DURING INTENSIVE GOLD THERAPY*

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IN THE course of a study of intensive chrysotherapy with aurothioglycanilide (lauron) already reported,[1] serial hematologic observations revealed a constant and often striking increase in the esoinophil count, which is the subject of this report.

MATERIAL AND METHODS

Eighteen patients were treated with bi-weekly injections of gold. Sixteen received aurothioglycanilide (lauron), 1 received solganol-B oleosum, and 1 received myochrysine. The total dosage given ranged from 1 gm. to 10 gm in a period of twenty-four to fifty-six days. Prior to every injection of gold, each patient received a complete blood count, platelet count and prothrombin-time determination.

TABLE 1. *Range of Eosinophilia in Relation to the Dosage of Gold and Duration of Treatment in 18 Patients Undergoing Intensive Chrysotherapy.*

PATIENT	DRUG	AMOUNT	EOSINOPHIL LEVEL		DURATION OF TREATMENT	DAY OF MAXIMUM EOSINOPHILIA
			INITIAL	MAXIMUM		
		gm.	*%*	*%*	*days*	
A. L.	Lauron	10.0	2	9	49	22
R. A.	Lauron	10.0	5	6	56	56
L. D.	Lauron	10.0	0	17	49	45
A. W.	Lauron	10.0	2	17	50	18
C. S.	Lauron	10.0	1	5	49	15
G. K.	Lauron	10.0	1	43	49	31
M. A.	Lauron	10.0	2	22	49	31
J. S.	Lauron	10.0	0	13	45	39
A. C.	Lauron	3.0	2	5	56	24
H. B.	Lauron	3.0	2	10	56	16
B. H.	Lauron	3.0	4	9	24	19
R. C.	Lauron	3.0	1	6	37	27
A. T.	Lauron	1.1	2	9	45	19
E. F.	Lauron	1.2	1	11	38	10
H. K.	Lauron	1.1	2	12	38	29
V. H.	Lauron	0.9	4	8	35	21
A. M.	Solganol B	1.0	2	8	45	31
B. M.	Myochrysine	1.0	1	5	49	10

RESULTS

No toxic reactions in the blood were observed with reference to any component. A constant increase in the eosinophil count was observed in every patient, and in all but 3 cases the maximum eosinophil count was in excess of 5 per cent of all white cells — a figure chosen as the upper limit of normal. The intensity of eosinophilia was not related to the amount of gold received or the duration of therapy (Table 1). The maximum eosinophil level occurred from ten days to fifty-six days after the start of therapy. In the patient who showed a count of 43 per cent during treatment an exfoliative dermatitis subsequently developed, but no other manifestations of toxicity occurred in the group. Although there was no direct correlation between the amount of drug received and the degree or time of appearance of eosinophilia, the mean eosinophil increase for 8 patients receiving 10 gm. of gold salt was 14.9 per cent, compared with 6.2 per cent for 10 patients who received 3 gm. or less.

TABLE 2. *Eosinophil Responses and Toxicity in 33 Patients Treated with Gold on an Outpatient Basis.*

GOLD PREPARATION	NO. OF PATIENTS TREATED	PATIENTS WITH EOSINOPHIL COUNTS OF MORE THAN 5 PER CENT	NO. OF TOXIC REACTIONS
Aurothioglycanilide	15	9	4
Gold sodium thiosulfate	13	3	2
Other types	5	0	2
	33	12	8

As a result of this experience the records of 33 consecutive patients treated with gold salts in the arthritis clinic as outpatients were reviewed, with reference to eosinophilia and toxic reactions. The results are shown in Table 2. Of 15 patients treated with aurothioglycanilide, 9 showed eosinophil counts in excess of 5 per cent, compared with 3 of 18 given other gold preparations. There was no significant difference in the frequency of toxic reactions in the two groups. The mean total dose of aurothioglycanilide employed was 1.99 gm., compared with 0.72 gm. of other forms of gold, chiefly gold sodium thiosulfate.

DISCUSSION

Eosinophilia as an accompaniment of chrysotherapy has long been recognized, and the subject is thoroughly reviewed by Sundelin.[2] Opinion is equally divided in the literature concerning whether or not eosinophilia is a contraindication to further gold therapy. Some observers regard it as a favorable prognostic sign.[3] The most careful study is that of Sundelin, and his conclusions based on an analysis of 700 cases were that eosinophilia was no contraindication to further gold therapy, since it often subsided while therapy was continued. In

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patients with eosinophilia all kinds of complications of gold therapy were more prevalent, but in many cases the eosinophilia occurred after the complication and could not, therefore, be used as a warning of its imminence.

Eosinophilia has been observed in the course of streptomycin therapy,[4] liver therapy of pernicious anema[5] and the administration of many other therapeutic substances. It can be produced in animals by the injection of heavy metals.[6] Some eosinophilia is a common occurrence in allergic and hyperergic states. It is generally accepted that the eosinophils play some role in the response to sensitization to foreign proteins. Recent reports suggest that this mechanism works through the endocrine system via the adrenal cortex.[7] Steinberg[8] has advocated serial bone-marrow studies during chrysotherapy as a guide to therapy. Since the significance of eosinophilia during gold therapy is still in question, we do not consider such a procedure warranted.

In our cases, although there was no direct relation in any case between the eosinophil level and the duration or intensity of treatment, the groups receiving larger amounts of gold showed a greater eosinophil increase. The frequency of eosinophilia was clearly higher in the patients receiving aurothioglycanilide, which again was probably due to the larger amounts of gold that were given with this preparation. In this short series of patients there was no greater frequency of toxicity in the aurothioglycanilide group despite the greater eosinophilia. Our observations agree with the conclusions of Sundelin that although marked eosinophilia should excite caution it is not a contraindication to further treatment that is otherwise indicated.

Summary

In 18 patients receiving intensive chrysotherapy, eosinophil counts from 5 to 45 per cent were observed in all cases.

This was not related to individual dosage or duration of treatment, but, as a general rule, the patients receiving more gold showed a higher mean eosinophil increase.

There was no direct relation between eosinophilia and toxic reactions, although the 1 case of exfoliative dermatitis encountered developed in the patient with the maximum increase of eosinophils.

References

1. Friedman, H. H., and Steinbrocker, O. Intensive chrysotherapy with aurothioglycanilide (lauron) in rheumatoid arthritis. *New Eng. J. Med.* **240**:362-366, 1949.
2. Sundelin, F. Die Goldbehandlung der chronischen Arthritis und besonderer Berücksichtigung der Komplikationen. *Acta med. Scandinav.* (Supp. **117**) pp. 1-291, 1941.
3. Mirick, G. S. Total agranulocytosis following gold therapy: report of case with recovery and review of literature. *Am. Rev. Tuberc.* **41**:344-357, 1940.
4. Arany, L. S. Streptomycin and eosinophilia. *J. A. M. A.* **135**:180, 1947.
5. Allin, R. N., and Meyer, O. O. Development of eosinophilia following liver therapy. *J. Lab. & Clin. Med.* **26**:457-463, 1940.
6. Piotrowski, G. Modifications sanguines au cours de la chrysothérapie. *Helvet. med. Acta* **2**:590-597, 1935.
7. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G. Test for adrenal cortical insufficiency: response to pituitary adrenocorticotropic hormone. *J. A. M. A.* **137**:1005-1009, 1948.
8. Steinberg, C. L. Gold toxicity in rheumatoid arthritis with particular emphasis on bone-marrow study. *Ann. Rheumat. Dis.* **7**:256, 1948.

MEDICAL PROGRESS

NEUROPHYSIOLOGY, 1942 - 1948*

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THE war years gave valuable impetus to studies on the nervous system, but few of the many important advances during these years stemmed from wartime research per se. The subject of neurophysiology has come to have such vast ramifications that it would be imprudent to attempt to cover the entire field in a brief review. I propose, therefore, to restrict this summary to the newer disclosures in the motor sphere. Developments in sensory physiology must be relegated to another occasion and a better informed reviewer, and likewise the many studies on the special senses, particularly the notable work on night vision carried out in Sweden, England and the United States. In planning the present summary I have followed in general the subject sequence of my monograph, *Physiology of the Nervous System*,[1] but I have included nothing described therein, except on occasion for historical setting.

MOTOR UNITS

In 1929 Denny-Brown[2] observed that when a single unit of a muscle, such as the cat's soleus, was activated, the muscle as a whole might develop as much as 10 gm. of tension. In their classic paper on the motor unit published in 1930, Eccles and Sherrington[3] obtained similar average values — that is, after maximal stimulation of the muscle and recording of the total tension developed, the motor fibers supplying the muscle were enumerated; by division of the number of fibers into the total tension, average figures were obtained of 5 to 10 gm. for soleus, and as much as 30 gm. for the medial head of the gastrocnemius. Clark[4] counted the muscle fibers in the preparations that Eccles and Sherrington had used and found that each nerve fiber innervates from 100 to 150 muscle fibers, thus accounting for the relatively large tension capable of being developed by single ventral-horn cells. Eccles and Sherrington were aware of the fact that there were large differences in nerve-fiber diameters, and they assumed that the large fibers innervated large units and that the smaller ones probably innervated lesser units. They incidentally proved conclusively that the small fibers (some only 2 or 3 microns) come from the ventral horn and not from the sympathetic chain.

Recently, Kuffler and his associates,[5, 6] working on frogs, have suggested that the small-nerve motor system of the skeletal musculature belongs to a special reflex group and that it can be activated independently of the large-fiber system. According to Kuffler et al., the large-fiber system produces the quick-twitch response with a single volley, whereas the small-fiber system causes appreciable muscle shortening only on repetitive excitation. The shortening is said to be "local" although considerable tension can be generated. The authors believe that a given muscle fiber may be innervated by both the small and the large fibers, but they add that this anatomic detail has not yet been conclusively demonstrated. They believe that, depending upon which fiber system stimulates the muscle, the muscle itself responds either with a local slow shortening or by a rapid shortening from a propagated disturbance. They draw the general conclusion that the large-fiber system is designed for rapid phasic movements, and the small-fiber for prolonged states of tension such as would be required for the maintenance of posture. Their hypothesis thus implies that a simple muscle fiber could be made to execute a sustained postural contraction at one time or a quick, all-or-none, twitch-like contraction at another.

Kuffler's observations as such are of considerable interest, particularly on account of his ingenuity in separating, both by reflex means and by compression of the nerve trunk, the large-fiber impulses from those of smaller diameter. The interpretations placed on the observations stand as a reversion to the long-abandoned dualistic theory of muscle function — that is, there are two sets of peripheral mechanisms, one for the execution of phasic movement and the other for postural tone, in the same muscle fiber. To be sure, many muscles have rapid white fibers admixed with slower-acting red fibers, and Denny-Brown[7] clearly demonstrated that the slower red fibers are selectively employed for maintenance of postures, but they are activated in all-or-none fashion just as the white fibers.

An alternative explanation of Kuffler's findings suggests itself: if the small-fiber system innervates fewer muscle fibers than the large-fiber system, one would anticipate that repetitive stimulation would be necessary to develop measurable tension at the tendon. This leaves unexplained Dr. Kuffler's claim

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that the action potentials developed at the end plates of the small-fiber system are not propagated. If this is borne out in future work, Kuffler and Gerard have presented the physiologic world with a conundrum that will occupy neurophysiologists for some years to come.

A more plausible explanation of the effects of small-fiber stimulation has been offered by Leksell,[8] who has succeeded in selectively stimulating these small-fiber units (gamma fibers) in both cats and frogs. He was unable to detect any certain contractile effects that could not have been attributed to unblocked large fibers, but he found that with the muscle taut, stimulation of the gamma fibers had a definite effect on the afferent discharge from the muscle's proprioceptors:

> Selective activation of the gamma fibers led to a considerable increase in afferent discharge provided the muscle was subjected to a certain amount of stretch. In slack muscles this effect did not appear. It is concluded that the gamma fibers serve as regulators of sensory activity originating in the muscle.

Sherrington, in 1894, had found that small fibers of the ventral roots innervated the muscle spindles. Until more forceful contrary evidence is presented than that offered by Kuffler et al. it seems reasonable to conclude either that the small motor fibers innervate the muscle spindles and thus regulate proprioceptive afferent discharge, as Leksell has suggested, or that they are all-or-none motor fibers innervating small skeletal-muscle units. The Kuffler-Gerard evidence that the small fibers are concerned with postural contraction except as they may influence the stretch receptors appears to me unconvincing.

Isolation of single units has also been achieved for human nerve and muscle by Kugelberg and Skoglund.[9] Using two muscles, the first dorsal interosseus (stimulated through the ulnar nerve at the elbow) and the peroneus (stimulated through the peroneal nerve at knee level), they have been able to compare artificially evoked responses from nerve stimulation with the natural discharges of single motoneurons of the same muscle during voluntary contraction. They find, on nerve stimulation with slowly rising currents, that small spikes appear first, followed later by larger ones, which correspond to the units of higher threshold (and presumably of larger size).* Precisely the same sequence was observed on volitional activation of these muscles—that is, small, low-threshold units discharged first, followed later by the larger, high-threshold units. The work of Kugelberg and Skoglund appears particularly significant since it indicates that some, at least, of the smaller units (which, one may assume, are innervated by nerve fibers of small diameter) give rise to all-or-none contractions. This, however, does not preclude the possibility that othere are concerned with proprioceptive regulation as Leksell[8] has suggested.

*Kugelberg and Skoglund[9] are unwilling to commit themselves regarding whether there is a direct relation between spike size and unit size. Although such caution is commendable, it would be contrary to all that is known of electrophysiology if there were not a direct relation.

The Spinal Cord

The human spinal cord was intensively studied during the war period owing to the large number of cases of spinal injury that came under observation in military establishments. During World War I a spinal transection was equivalent to a death sentence. A few patients survived for periods of a year or two as a result of fastidious nursing care, but the great majority succumbed to bedsores and ascending genitourinary infections within a few weeks of injury. Through the work of the late George Riddoch[10, 11] in 1916–1917 the way was pointed for adequate care of such patients — how through the development of the bladder reflexes, the bladder itself could be kept free of infection and, through careful nursing, the skin could be kept clear and healthy. Now with the powerful adjunct of the sulfonamides, penicillin and streptomycin it has become possible to keep patients with spinal paraplegia healthy and free of infection for indefinite periods. With this therapeutic triumph has come increasing knowledge of the reflex status of spinal man.

Thanks to the work of Freeman,[12] Deaver,[13] Munro[14] and others who have studied more than a thousand cases of spinal injury during the war period, it is clearly established not only that flexor reflexes and mass withdrawal reactions return, but also that knee jerks and other strongly developed extensor reflexes may be regained and that they may be put to useful purpose in rehabilitating such patients and in making them ambulatory. During World War I it would not have been thought possible for a patient with complete spinal transection to become ambulatory and capable of attending to his own rectal and bladder functions. One of Freeman's patients, wounded in World War II, dresses himself in the morning, attends to his own toilet, swings himself on crutches into his own car and drives to work. Fiercely proud of his independence he declines assistance at any point of his daily routine. As a watchmaker he has an income of between three and four thousand dollars a year. In Dr. Freeman's series there are 30 other patients with spinal paraplegia that are similarly self-reliant and self-supporting. In the past there has been nothing more hopeless or pitiable than cases of spinal transection. Now, as the result of intelligent application of sound physiologic principles, such patients have reasonable hope for a useful life, and there are several authentic cases of women with complete spinal transection who have conceived and borne normal offspring.[15, 16] Ambulation technics such as those described by Deaver, combined with diligent bladder care and other observances of detail in management, have enabled

more than half the patients with spinal injuries sustained in the war to find a place in society.

Hope for promoting regeneration in the severed spinal cord still haunts the imagination of neurologists and neurosurgeons, and Freeman is of the belief that ways and means will be found to bring about voluntary control of musculature distal to a spinal transection. Sugar and Gerard[17] report that they have obtained regeneration in the spinal cords of rats, but Davidoff and Ransohoff[18] have been unable to confirm their results in cats. Brown and McCouch,[19] similarly have failed to obtain evidence of cord regeneration in dogs and cats even when the cut ends of the cord were sealed together with prothrombin. The late Richard Meagher and Franc Ingraham, in unpublished studies, believed that they had bridged the gap in spinal puppies by planting an intercostal nerve rootlet from above the transection into the distal cut end of the spinal cord. Their histologic results were, however, unsatisfactory, and publication was on this account withheld. Freeman[12] describes a patient with transplanted spinal roots who has developed paresthesias and muscular twitchings in segments below the transection a year after operation.

The Thalamus

There have been few physiologic contributions to the knowledge of thalamic function since the publication of Earl Walker's[20] monograph, *The Primate Thalamus*, published in 1938. The projections to and from the dorsomedial nucleus of the thalamus and the rostral areas of the frontal lobes, and particularly from areas 9, 10, 11 and 12 of Brodmann and possibly from Walker's area 13 (Glees[21]), indicate that the dorsomedial nuclei are concerned with the effects induced by the operation of frontal lobotomy. Especially relevant in this connection is the fact that the operation has been used extensively for the relief of intractable pain, and it thus appears that the medial nuclei are in some way concerned with establishing the general character of pain reaction, but the precise nature of this relation remains to be worked out. After frontal lobotomy and the presumed degeneration of the dorsomedial nuclei that follows (Freeman and Watts[22]), patients state that they still feel their pain but that it has ceased to bother them.[23]

The large nucleus ventralis posterolateralis (VPL), which is the chief end station for the spinothalamic projections, has been studied in some detail by Chang and Ruch[24] in the spider monkey. Walker and others had previously shown a high degree of topographical lamination from the various spinal segments, the cervical being situated most medially and the sacral segment most laterally. The spider monkey, in addition to the usual lumbar segments, has three sacral roots and a caudal plexus usually made up of eight caudal roots that innervate the complex musculature of the prehensile tail. The dermatomes for the tail were carefully mapped by Sherrington's method of "remaining sensibility," and the degeneration resulting from dorsal root section and from section of caudal segments of the spinal cord were traced by Chang and Ruch[25] up the spinal cord into the dorsal column and into the thalamus. It was found that the large caudal projections to the thalamus were located in a sharply defined, comma-shaped area lying just lateral to the sacral projections (Fig. 1). Thus, in the spider monkey, one finds an even more precise topographical representation in the thalamus than in forms that lack the extra prehensile appendage.

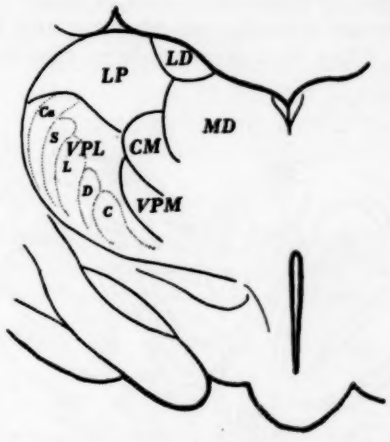

Figure 1. *Diagram Showing the Topographic Arrangement in the Thalamus of the Spinothalamic Fibers from Different Levels of the Spinal Cord in the Spider Monkey.*

LP = *nucleus lateralis posterior*; LD = *nucleus lateralis dorsalis*; CM = *centrum medianum*; MD = *nucleus medialis dorsalis*; VPM = *nucleus ventralis posteromedialis*; VPL = *nucleus ventralis posterolateralis*; Ca = *caudal projections*; S = *sacral*; L = *lumbar*; D = *dorsal* (*thoracic*); C = *cervical*. (*Reproduced from Chang and Ruch,*[24] *with permission of the publishers.*)

The Hypothalamus

There have been few notable advances in knowledge of hypothalamic function since the publication in 1940 of the hypothalamus volume of the Association for Research in Nervous and Mental Disease, except for the recent disclosures concerning sham rage and for certain developments in the sphere of heat regulation and metabolism.

Sham Rage

Wheatley[26] has found that sham rage may be induced in enduring fashion in cats through placement of bilateral Horsley–Clarke lesions in the nucleus hypothalamicus ventromedialis — that is, in the infundibular or middle region of the hypothalamus. Lesions in this region also interrupt the large tract of pallidohypothalamic (Fig. 2) fibers, as well as part of the fornix column. Wheatley's animals behaved in closely similar fashion to those of Fulton and Ingraham[27] after bilateral prechiasmal

lesions made by direct surgical interference. It was not clear from these studies, however, exactly what pathways or centers must be interfered with, but Wheatley's experiments have greatly reduced the possible alternatives. Kennard[28] has induced conspicuous sham rage in cats by radical removal of both frontal lobes; she also observed it in animals in which only the orbital surface was involved, but it is not clear from her protocols whether the rhinencephalon or its projections had been encroached upon.

Quite recently Bard and Mountcastle[29] have offered a highly significant body of data — if indeed they have not actually solved the major anatomic problem. They find it possible in cats to remove the entire neocortex (both sides) and then observe that such a decorticate preparation shows no sign of anger or affect even when subjected to severe nociceptive stimulation such as pinching of the tail with heavy forceps. Unless the stimulation becomes exceedingly intense, the animal usually purrs, and its general behavior is that of an animal responding to pleasurable stimulation irrespective of whether the stimulus would normally be pleasurable or not.

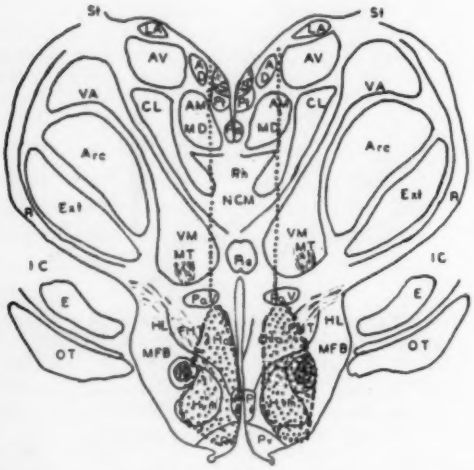

FIGURE 2. *Diagram Showing Restricted Lesions in the Two Ventromedial Hypothalamic Nuclei* (Hvm).

PHT = *pallidohypothalamic tract*; Ha = *anterior hypothalamic area*; MFB = *median forebrain bundle*; HL = *nucleus hypothalamicus lateralis*; PaV = *nucleus hypothalamicus paraventricularis*. (*Other abbreviations are explained by Wheatley*[26] *in his Figure 13.*)

If, however, the rhinencephalon is involved bilaterally, an animal that previously showed pleasurable reactions immediately shows the sham-rage pattern of behavior to any form of stimulation. These important findings, which were communicated in December, 1947, at the meeting of the Association for Research in Nervous and Mental Disease, indicate that the mechanisms of emotional expression are normally under the control of the olfactory center of the brain and that the hypothalamic centers normally governed by this region begin to discharge uncontrollably once connection is severed between them. It is not yet clear, however, how the autonomic centers in the neocortex correlate their activities with that of the rhinencephalon on the one hand, and with the hypothalamus on the other. As pointed out elsewhere in this review, there is evidence of close functional connection between the orbital surface – that is, area 13, which is a part of the neocortex — and the posterior hypothalamic nuclei, but there is still little evidence pointing to which nuclei in the hypothalamus receive projections from the rhinencephalon.

Kidney Function

Harris,[30] in a detailed study of the effects of stimulating the hypothalamus at the site of origin of the pituitary stalk (through the use of an implanted electrode activated by remote control), was able to induce in conscious rabbits sharp inhibition of a water diuresis, increase in urinary chloride and marked increase in estrus. These three effects could be duplicated by intravenous injection of posterior-lobe extracts. This is in keeping with the studies of Mary Pickford,[31] who finds that application of small quantities of acetylcholine (for example, 8 microgm.) to the supraoptic nucleus and to no other part of the hypothalamus causes prompt suppression of the diuresis through stimulation of the supraopticohypophysial system. The effect was augmented by eserine salicylate and removal of the pituitary body abolished it. These studies afford further evidence of the part that the nervous system plays in regulation of kidney functions.

Metabolic Functions

That other visceral and metabolic functions are regulated by the nervous system is also evident from the studies of Brobeck,[32, 33] who describes important neurogenic factors in the genesis of obesity. In his review he points out that Hetherington and Ranson, in 1939, succeeded in confirming beyond doubt the observations of Bailey and Bremer that lesions confined to the hypothalamus may produce obesity whether or not the pituitary body is damaged. Earlier studies had pointed toward the same conclusion, but of all those who investigated the problem, only Hetherington and Ranson were able to prepare animals with lesions that completely spared the hypophysis. Only their data, therefore, appeared unequivocal. After the appearance of Hetherington and Ranson's report, Brobeck[32] began to study the nature of the deficit responsible for the obesity — that is, the source of the energy surplus that leads to the accumulation of the large quantity of fat. It now seems to be generally agreed that most of this extra energy is derived from ingestion of an excessive quantity of food, and that

the most important deficit exhibited by the affected animals concerns their regulation of food intake. The degree of the obesity appears to be a measure of the severity of the overeating. This is true in all species thus far studied — in rats, cats, dogs and monkeys.[33, 34]

There is, however, certain evidence that overeating, or hyperphagia, is not the only disturbance present, since certain animals with hypothalamic lesions tend to gain weight because of a depression of either basal heat production or energy output as locomotor activity. But Brobeck in 1946 found that neither of these changes contributes significantly to the development of obesity in animals fed ad libitum, inasmuch as both the basal heat production and total energy output tend progressively to rise above normal levels as animals become obese. Only when food intake is restricted do reduced activity and basal heat loss lead to an abnormal gain of weight.

Since lesions of the hypothalamus may interfere with regulation of each of the four factors involved in energy exchange — namely, food intake, activity, heat loss and body weight — it follows that the hypothalamus must be the level at which processes of energy metabolism are regulated and integrated by the central nervous system.

The Frontal Lobes

No part of the brain has received a larger share of attention during the past five years than the frontal lobes. This has been due, in large measure, to the growing interest in the operation of frontal lobotomy, inaugurated in 1935–1936 by Egas Moniz, of Lisbon,[35] and introduced into the United States the following year by Freeman and Watts,[36] who in 1942 published their much discussed monograph.[37] The operation had its origin in a preliminary communication given in 1935 before the International Neurological Congress in London on the behavioral changes observed in 2 chimpanzees after bilateral removal of the forepart of the frontal lobes.[38] After the procedure the animals failed to exhibit frustrational behavior, temper tantrums and so forth, and Professor Moniz, on the basis of this admittedly imperfect evidence, concluded that interruption of the projection systems from the more forward of the frontal areas might relieve anxiety states in man. Removal of the forepart of the frontal lobes in the chimpanzees had been extensive, involving areas 9 and 10, and parts of 11 and 12 of Brodmann,[39] but it had not encroached upon the orbital surface, now designated areas 13 and 14 in Walker's[40] modification of the Brodmann scheme. From the experimental standpoint, therefore, there was no clear-cut indication of what part of the 9, 10, 11 and 12 complex need be removed to abolish frustrational behavior. It is also probable that areas 24 and 25 on the cingulate gyrus were involved, the rhinencephalon thus being brought into the picture.

Despite absence of such basic experimental data, the lobotomists have gone ahead, and it is estimated that by January 1949 nearly 10,000 radical lobotomies had been performed in the United States and England and on the Continent. Penfield[41] and his colleagues at Montreal,[42] although recognizing the potential value of the operation, have been more conservative and have carried out a number of gyrectomies involving various parts of the frontal lobe in the hope of obtaining more precise evidence of the region concerned in the relief of anxiety states. His cases, as reported in December, 1947, are still too few to admit of precise evaluation, but it appears that areas 10 and 12 on the lateral surface have little influence, the more medial projections probably being the ones most intimately concerned.

Area 24

The anterior portion of the cingular gyrus, known in the older literature as the anterior limbic area and in Brodmann's map as area 24 (Fig. 3), had been little studied until recently, but it was generally thought to be part of the rhinencephalon and therefore olfactory in function. Wilbur K. Smith[43] discovered that it had autonomic affinities, for on stimulation he obtained dilatation of the pupils, piloerection and cardiovascular changes that consisted of either an abrupt fall of pressure and slowing of the pulse or a slow rise with acceleration of the pulse, depending upon what part was stimulated. As with area 13, respiratory arrest generally occurred on excitation of area 24, with widespread relaxation of the skeletal musculature. McCulloch,[44] independently of Smith, had found that strychninization of area 24 led to relaxation of existing mus-

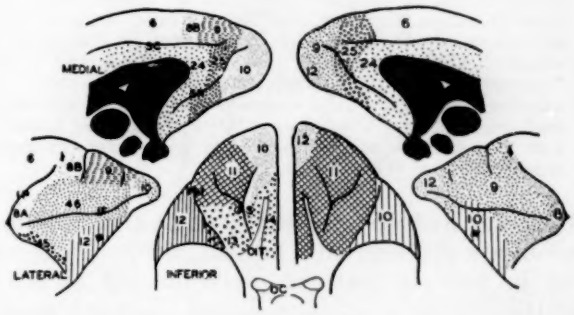

FIGURE 3. *Walker's[40] Modification of Brodmann's[39] Map. Walker's cytoarchitectural map of the prefrontal lobe of* Macaca mulatta *(left) is compared with Brodmann's map of* Cercopithecus *(right). The numerical designations in Walker's map are derived from Brodmann's designations of comparable areas in the human cerebral cortex and hence do not necessarily have anything in common with Brodmann and Vogt's designations for the monkey.*

.cular contraction, holding in abeyance of motor afterdischarge and suppression of motor response to stimulation of any motor focus in the cerebral cortex. Area 24 is thus to be classified with areas 4s, 8s and 2s as a powerful suppressor region. Smith also described vocalization as one of the effects of stimulating area 24, but this was not noted by McCulloch or by Ward[45] in his more recent study of the cingular gyrus. He has, however, confirmed Smith and McCulloch in all other details.

Ward[45] has also studied the effects of ablating area 24 in a group of monkeys. The behavioral changes were striking, and the animals after such a lesion, particularly if it were bilateral, appeared to lose "social conscience" thus:

> Immediately following either unilateral or bilateral subpial resection of the rostral cingular gyrus in the monkey there is an obvious change in personality. The monkey loses its preoperative shyness and is less fearful of man. It appears more inquisitive than the normal monkey of the same age. In a large cage with other monkeys of the same size, such an animal shows no grooming behavior or acts of affection toward its companions. In fact, it treats them as it treats inanimate objects and will walk on them, bump into them if they happen to be in the way and will even sit on them. It will openly eat food in the hand of a companion without being prepared to do battle and appears surprised when it is rebuffed. Such an animal never shows actual hostility to its fellows. It neither fights nor tries to escape when removed from a cage. It acts under all circumstances as though it had lost its "social conscience." [This is probably what Smith[46] saw and called "tameness."] It is thus evident that following removal of the anterior limbic area, such monkeys lose some of the social fear and anxiety which normally governs their activity and thus lose the ability to accurately forecast the social repercussions of their own actions.

Ward has had the opportunity of making a similar lesion in a degenerated schizophrenic human being, and he believes that the procedure did as much for the patient as a more radical lobotomy would have done. Further studies on the effect of regional ablation of the cingulate are urgently needed both in animals and in man.

Area 13

More precise localizing data have been obtained for the posterior orbital gyrus (area 13) and for the medial orbital gyrus (area 14). In 1894 Spencer[47] had found that faradic stimulation of the orbital gyrus caused profound changes in respiratory movements and also in the level of the systolic blood pressure — this being true in dogs, cats, rabbits and monkeys. The studies of Spencer, however, were lost sight of until rediscovered by Bailey and Sweet[48] in 1940. Meanwhile, Bailey and Bremer[49] had shown that stimulation of the central cut end of the vagus nerve in the isolated head caused marked changes in the electroencephalogram of the posterior orbital gyrus and in no other part of the cerebral mantle. They concluded that this region of the orbital surface contained the chief central representation of the autonomic system. In 1943 Ruch and Shenkin[50] carried out bilateral ablations of area 13 and found thereafter that the monkeys exhibited profound restlessness, pacing back and forth in their cages incessantly; when measured in activity cages, their motility was found to have increased 500 to 600 per cent.

More recently, Fulton, Livingston and Davis[51] have confirmed Ruch and Shenkin's results on the effects of ablation, and Delgado,[52] who studied their animals, has disclosed that skin temperature of the extremities and the ear lobes after bilateral removal of area 13 rises 8 to 10° and approaches the rectal temperature. In the light of this observation, Delgado suggests that the hypermotility that follows orbital gyrectomy may be a compensatory phenomena to assist in maintaining body temperature in the face of excessive heat loss. This release of vasoconstrictor tone must also cause a considerable decrease in peripheral resistance, which no doubt accounts for the rather striking falls in blood pressure that Freeman and Watts,[36, 37] and others, have reported after their lobotomies — for in the Watts operation the line of incision passes down to the sphenoidal ridge and thus involves the posterior orbital gyrus. It has been suggested, indeed, that orbital gyrectomy may be the operation of choice for the relief of essential hypertension.

Equally significant have been the studies of Delgado and Livingston,[53] and of Livingston, Chapman and Livingston[54] on the effects of stimulation of area 13 in animals and man, particularly their disclosure of the importance of rate of stimulation. Wyss,[55] of Geneva, had found that the effects on respiration of stimulating the central end of the vagus nerve varied profoundly with the rate at which the nerve was stimulated; thus, at 70 per second, breathing movements could be arrested at expiration whereas at 20 per second inspiratory effects were obtained; at other rates respiratory movements could be made to increase in both depth and rate. Since there had been some discrepancies in the earlier reports on stimulation of the orbital surface, Delgado and Livingston,[52, 53] in the light of Wyss's observation, studied the effect of changing the frequency of the stimulus and obtained results corresponding closely with those reported by Wyss for the central end of the vagus. The responsiveness not only of area 13 but also of the cortex in the depths of the presylvian sulcus varies with frequency. Thus, the latter was entirely unresponsive at the higher rates (180 per second), but began to give responses at 60 per second (slowing); at 6 per second there was respiratory arrest in inspiration, and at 30 per second augmentation of inspiratory and expiratory amplitude.

It had been reported in man that the orbital surface was completely unresponsive to electrical stimulation (Penfield, Foerster and so forth). The importance of controlling frequency, however, had not been appreciated, and Livingston and his colleagues, after having negative results when they

stimulated the orbital surface with a 60-cycle stimulator, found striking respiratory effects, such as those seen in Figure 4, when they stimulated at 10 per second, the electrodes being of the needle concentric type, thrust down to the orbital ridge through a leukotomy burr hole (with the patient under pentothal anesthesia). Other details concerning the responses of the human orbital gyrus stimulation are found in the legend of Figure 4. It will be noted that respiratory effects can be separated from vasomotor effects, the latter being most conspicuously obtained from the more medial foci on the orbital surface.

The pathways from area 13 have still to be worked out; the main projection appears to pass through

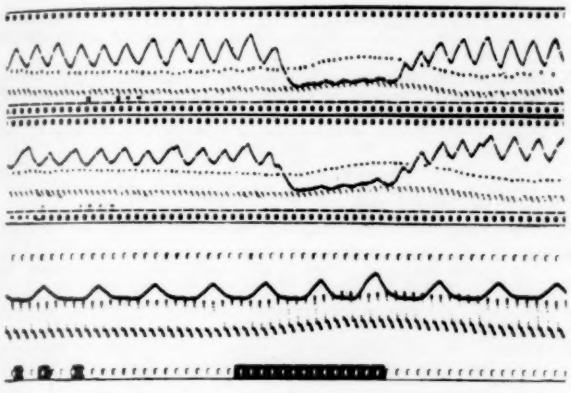

FIGURE 4. *Photographic Record of the Respiratory and Blood-Pressure Response (Femoral Artery) to Stimulation of the Orbital Surface of Man under Light Pentothal Anesthesia.*

All stimulations are of ten seconds' duration and are at 10 cycles per second. The signal at the bottom of each strip identifies and delimits onset and duration of stimuli. The first two strips show responses, from two different orbital loci, of prompt respiratory arrest in expiratory position and blood-pressure rise after a short latent period. The third strip shows the response in a region where no respiratory effect is obtained but where there is a moderate blood-pressure response. (Reproduced from Livingston, Chapman, Livingston and Kraintz[54] with permission of the publishers.)

the anterior end of the internal capsule, and thence to the supraoptic nuclei of the hypothalamus. Glees[56] has made a preliminary study of the anatomic degenerations following lesions in this region, and a large proportion of the fibers appear to be unmyelinated. Ward and McCulloch[57] find that when strychnine is injected into the orbital surface, the supraoptic nuclei, as well as some of the posterior hypothalamic ones, become specifically activated (Fig. 5). It thus seems probable that area 13 has primary subcortical connections with the hypothalamus.

Area 14

Less is known about functional localization in area 14 (medial orbital gyrus). Vasomotor responses are sometimes obtained on stimulation. Owing to its proximity to the olfactory nerve, it has been less carefully studied than the more lateral parts of the orbital surface. Fulton, Livingston and Davis[51] noted that when the posterior part of area 14 is incised bilaterally, the animals (monkeys)

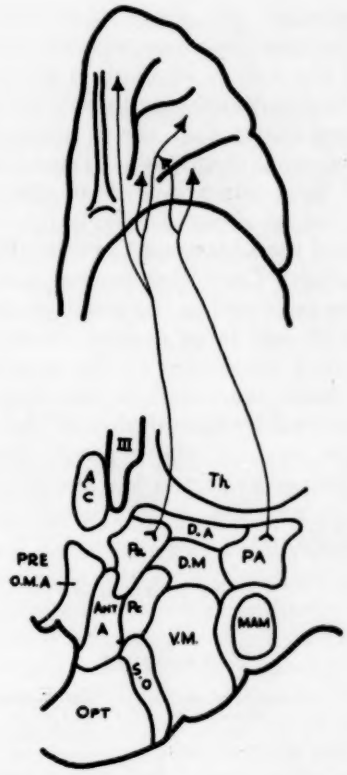

FIGURE 5. *Diagrammatic Representation of Homolateral Projections from Areas 13 and 14 (Orbital Gyrus) of the Monkey to the Hypothalamus.*

Pa = *paraventricular nucleus*; PA = *posterior hypothalamic area. (Other abbreviations are explained by Ward and McCulloch.*[57])

develop conspicuous sham rage similar to that described after corresponding lesions in cats by Fulton and Ingraham.[27] In their recent analysis of sham rage, Bard and Mountcastle[29] observed that the entire neopallium can be removed without the appearance of sham rage so long as the rhinencephalon remains intact. If, however, the rhinencephalon is encroached upon bilaterally, even though the neocortex remains intact, sham rage invariably occurs. It therefore appears that lesions of the posterior part of area 14 must interrupt projections to and from the rhinencephalon. Sham rage has not been encountered after bilateral lesions of area 13.

The fact that the orbital surface was spared in the 2 chimpanzees on which the operation of frontal lobotomy was based and the fact that profound autonomic changes develop when area 13 is involved and further that sham rage may follow posterior

lesions of 14, suggest that in the operation of frontal lobotomy, the orbital surface should be spared. The work of Ward indicates that more attention should be given to the specific function of the cingulate gyrus, which is known to be intimately associated with the olfactory center of the brain and hence with the emotional life of man.

Renal Circulation

It was pointed out above that the supraoptic nuclei in the hypothalamus regulate tubular reabsorption of the kidney through controlling the secretion of the posterior pituitary body, and it has recently been shown that the nervous system also regulates the renal circulation. Trueta and his colleagues[58, 59] have discovered that the glomerular circulation can be shunted reflexly into the medullary vessels of the kidney and so completely abolish urine formation. Cort[60] has proved that this renal shunt can be activated in the spinal animal through stimulation of any large sensory nerve, the reflex being abolished by section of the lesser splanchnic nerve. He finds, moreover, in cats that the shunt can be activated by stimulation of the vasomotor center in the medulla, the posterior hypothalamic nuclei and also areas 13 and 6 of the cerebral cortex. This clearly provides a physiologic explanation of emotional anuria.

(To be concluded)

References

1. Fulton, J. F. *Physiology of the Nervous System.* 684 pp. Third edition. New York: Oxford University Press, 1949.
2. Denny-Brown, D. E. Nature of postural reflexes. *Proc. Roy. Soc., London* (S.B.) **104**:253-301, 1929.
3. Eccles, J. C., and Sherrington, C. S. Numbers and contraction-values of individual motor-units examined in some muscles of limb. *Proc. Roy Soc., London* (S. B.) **106**:326-357, 1930.
4. Clark, D. A. Muscle counts of motor units: study in innervation ratios. *Am. J. Physiol.* **96**:296-304, 1931.
5. Kuffler, S. W., and Gerard, R. W. Small-nerve motor system to skeletal muscle. *J. Neurophysiol.* **10**:383-394, 1947.
6. Kuffler, S. W., Laporte, Y., and Ransmeier, R. E. Function of frog's small-nerve motor system. *J. Neurophysiol.* **10**:395-408, 1947.
7. Denny-Brown, D. E. Histological features of striped muscle in relation to its functional activity. *Proc. Roy. Soc., London* (S.B.) **104**:371-411, 1929.
8. Leksell, L. Action potential and excitatory effects of small ventral root fibres to skeletal muscle. *Acta physiol. Scandinav.* **10** (Supp. 31): 1-84, 1945.
9. Kugelberg, E., and Skoglund, C. R. Responses of single human motor units to electrical stimulation. *J. Neurophysiol.* **9**:391-398, 1946. Natural and artificial activation of motor units—comparison. *Ibid.* **9**:399-412. 1946.
10. Riddoch, G. Reflex functions of completely divided spinal cord in man, compared with those associated with less severe lesions. *Brain* **40**:264-402, 1917.
11. Head, H., and Riddoch, G. Automatic bladder, excessive sweating and some other reflex conditions, in gross injuries of spinal cord. *Brain* **40**:188-263, 1917.
12. Freeman, L. W. Personal communication.
13. Deaver, G. G. and Brown, M. E. Challenge of crutches: standard crutch gaits and how to teach them. *Arch. Phys. Med.* **26**:573-582, 1945.
14. Munro, D. Rehabilitation of patients totally paralyzed below waist, with special reference to making them ambulatory and capable of earning their own living. II. Control of urination. *New Eng. J. Med.* **234**:207-216, 1946.
15. Elkin, D. C. Spontaneous labor in case of decentralized uterus. *J. A. M. A.* **78**:27-29, 1922.
16. Reynolds, S. R. M. *Physiology of the Uterus with Clinical Correlations.* 447 pp. New York: Paul B. Hoeber, Inc., 1939.
17. Sugar, O., and Gerard, R. W. Spinal cord regeneration in rat. *J. Neurophysiol.* **3**:1-19, 1940.
18. Davidoff, L., and Ransohoff, J. Absence of spinal cord regeneration in cat. *J. Neurophysiol.* **11**:9-11, 1948.
19. Brown, J. O., and McCouch, G. D. Abortive regeneration of transected spinal cord. *J. Comp. Neurol.* **87**:131-137, 1947.
20. Walker, A. E. *The Primate Thalamus.* 344 pp. Chicago: University of Chicago Press, 1938.
21. Glees, P. Significance of frontal lobe connections in mental diseases. *Experientia* **3**:394-397, 1947.
22. Freeman, W., and Watts, J. W. Retrograde degeneration of thalamus following prefrontal lobotomy. *J. Comp. Neurol.* **86**:65-93, 1947.
23. Watts, J. W., and Freeman, W. Frontal lobotomy in treatment of unbearable pain. *Research Publ. A. Nerv. & Ment. Dis.* **27**:715-722, 1948.
24. Chang, H. T., and Ruch, T. C. Topographical distribution of spinothalamic fibres in thalamus of spider monkey. *J. Anat.* **81**:150-164, 1947.
25. *Idem.* Morphology of spinal cord, spinal nerves, caudal plexus, tail segmentation, and caudal musculature of spider monkey. *Yale J. Biol. & Med.* **19**:345-377, 1947.
26. Wheatley, M. D. Hypothalamus and affective behavior in cats: study of effects of experimental lesions, with anatomic correlations. *Arch. Neurol. & Psychiat.* **52**:296-316, 1944.
27. Fulton, J. F., and Ingraham, F. D. Emotional disturbances following experimental lesions of base of brain (pre-chiasmal). *J. Physiol.* **67**:xxvii, 1929.
28. Kennard, M. A. Focal autonomic representation in cortex and its relation to sham rage. *J. Neuropath. & Exper. Neurol.* **4**:295-304, 1945.
29. Bard, P., and Mountcastle, V. B. Some forebrain mechanisms in expression of anger. *Research Publ. A. Nerv. & Ment. Dis.* **27**: 362-404, 1948.
30. Harris, G. W. Innervation and actions of neurohypophysis: investigation using method of remote-control stimulation. *Philos. Tr.* **232***B*:385-441, 1947.
31. Pickford, M. Action of acetylcholine in supraoptic nucleus of chloralosed dog. *J. Physiol.* **106**:264-270, 1947.
32. Brobeck, J. R. Effects of variations in activity, food intake and environmental temperature on weight gain in albino rat. *Am. J Physiol.* **143**:1-5, 1945.
33. *Idem.* Physiology of heat and cold. *Ann. Rev. Physiol.* **8**:65-88, 1946.
34. Strominger, J. L. Relation between water intake and food intake in normal rats and in rats with hypothalamic hyperphagia. *Yale J. Biol. & Med.* **19**:279-288, 1947.
35. Moniz, E. *Tentatives opératoires dans le traitement de certaines psychoses* 248 pp. Paris: Masson et Cie, 1936.
36. Freeman, W., and Watts, J. W. Prefrontal lobotomy in agitated depression: report of case. *M. Ann. District of Columbia* **5**:326-328, 1936.
37. *Idem. Psychosurgery: Intelligence, emotion and social behavior following prefrontal lobotomy for mental disorders.* With special psychometric and personality profile studies by Thelma Hunt. 337 pp. Springfield, Ill.: Charles C Thomas, 1942.
38. Fulton, J. F., and Jacobsen, C. F. Functions of frontal lobes: comparative study in monkeys, chimpanzees and man. *Abstr. Second Internat. Neurol. Congress, London,* 1935. P. 70.
39. Brodmann, K. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues.* 324 pp. Leipzig: J. A. Barth, 1909.
40. Walker, A. E. Cytoarchitectural study of prefrontal area of macaque monkey. *J. Comp. Neurol.* **73**:59-86, 1940.
41. Penfield, W. Bilateral frontal gyrectomy. A. Surgery. *Research Publ. A. Nerv. & Ment. Dis.* **27**:519-534, 1948.
42. Malmo, R. B. Bilateral fronta gyrectomy. C. Psychological assessments. *Research Publ. A. Nerv. & Ment. Dis.* (in press).
43. Smith, W. K. Functional significance of rostral cingular cortex as revealed by its response to electrical excitation. *J. Neurophysiol.* **8**:241-255, 1945.
44. McCulloch, W. S. Cortico-cortical connections. In Bucy, P. C. *The Precentral Motor Cortex.* Vol. 4. 605 pp. Urbana: University of Illinois Press, 1944. Chap. 8.
45. Ward, A. A., Jr. Cingular gyrus: area 24. *J. Neurophysiol.* **11**:13-23, 1948. Anterior cingular gyrus and personality. *Research Publ. A. Nerv. & Ment. Dis.* **27**:438-445, 1948.
46. Smith, W. K. Results of ablation of cingular region of cerebral cortex *Federation Proc.* **3**:42, 1944.
47. Spencer, W. G. Effect produced upon respiration by faradic excitation of cerebrum in monkey, dog, cat and rabbit. *Philos. Tr.* **185***B*: 609-657, 1894.
48. Bailey, P., and Sweet, W. H. Effects on respiration, blood pressure and gastric motility of stimulation of orbital surface of frontal lobe. *J. Neurophysiol.* **3**:276-281, 1940.
49. Bailey, P., and Bremer, F. Sensory cortical representation of vagus nerve, with note on effects of low blood pressure on cortical electrogram. *J. Neurophysiol.* **1**:405-412, 1938.
50. Ruch, T. C., and Shenkin, H. A. Relation of area 13 on orbital surface of frontal lobes to hyperactivity and hyperphagia in monkeys. *J. Neurophysiol.* **6**:349-360, 1943.
51. Fulton, J. F. Livingston, R. B., and Davis, G. D. Ablation of area 13 in primates. *Federation Proc.* **6**:108, 1947.
52. Delgado, J. M. R. Respiratory centers in frontal lobe. *Research Publ. A .Nerv. & Ment. Dis.* **27**:433-437, 1948.

53. Delgado, J. M. R., and Livingston, R. B. Some respiratory, vascular and thermal responses to stimulation of orbital surface of frontal lobe. *J. Neurophysiol.* **11**:39-55, 1948.
54. Livingston, R. B., Chapman, W. P., Livingston, K. E., and Kraintz, L. Stimulation of orbital surface of man during lobotomy. *Research Publ. A. Nerv. & Ment. Dis.* **27**:421-432, 1948.
55. Wyss, O. A. M. Respiratory effects from stimulation of afferent vagus nerve in monkey. *J. Neurophysiol.* **10**:315-320, 1947.
56. Glees, P. Personal communication and demonstration at 17th International Physiological Congress, Oxford, July, 1947.
57. Ward, A. A., Jr., and McCulloch, W. S. Projection of frontal lobe on hypothalamus. *J. Neurophysiol.* **10**:309-314, 1947.
58. Trueta, J., Daniel, P. M., Barclay, A. E., Franklin, K. J., and Prichard, M. M. L. Renal pathology in light of recent neurovascular studies: preliminary communication. *Lancet* **2**:237, 1946.
59. Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M., and Prichard, M. M. L. *Studies of the Renal Circulation.* 187 pp. Oxford: Blackwell Scientific Publications, 1947.
60. Cort, J. Unpublished data.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35221

PRESENTATION OF CASE

A thirty-nine-year-old woman was admitted to the hospital complaining of grossly bloody urine accompanied by small clots for one week.

During the same interval urinary frequency, dysuria and nocturia were present. In the week before admission she also had severe right-costovertebral-angle pain on motion of the right leg. There had been no leg edema, and no weight loss.

Her general health had always been good except for one episode of slight hematuria four years before admission.

Her menses were regular, with twenty-eight-day intervals. There had been no bleeding between periods, except for a two-week period two months before admission, when she bled "off and on."

Physical examination showed a nontender right-upper-quadrant mass. On pelvic examination a small mass was palpable on the posterior aspect of the uterus near the top.

The blood pressure was 120 systolic, 70 diastolic. The temperature was 98.8°F., the pulse 112, and the respirations 24.

The white-cell count was 6900, with 79 per cent neutrophils, 15 per cent lymphocytes, 3 per cent monocytes and 3 per cent eosinophils. The hemoglobin was 7.5 gm.

The specific gravity of the urine was 1.015, with a ++ test for albumin. The sediment contained 50 red cells and 25 white cells per high-power field. The urine culture was negative. The nonprotein nitrogen was 17 mg. per 100 cc.

On intravenous pyelography the kidneys were within normal limits as to size, shape and position. There was a soft-tissue swelling at the hilus of the right kidney, which appeared to be due to dilatation of the pelvis. After intravenous administration of dye, it was excreted promptly, outlining nondilated urinary passages on the left. Excretion on the right was slower, and there was dilatation of the calyxes on the right. The large, dilated pelvis showed only a small amount of dye in its margins, which suggested that the pelvis and the bases of the calyxes were filled by nonopaque material. The right ureter was not visualized. The bones of the lumbar spine and pelvis were not remarkable.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. SAMUEL VOSE: The picture of this case as presented in the abstract is that of a woman very seriously ill who had a mass in the region of the right kidney, gross hematuria and what was presumably an acute anemia (hemoglobin of 7.5 gm.), with a negative past history referable to the urinary tract except for one episode of slight bleeding four years previously and a small amount of vaginal bleeding two months prior to entry into the hospital. The bleeding must have been very severe to reduce the hemoglobin to this point. The laboratory findings are not particularly helpful except to demonstrate that she had anemia, and the intravenous pyelogram showed a filling defect in a hydronephrotic kidney.

Gross hematuria is one of the most important and interesting conditions that occur in disease of the urinary tract. Since there are some forty-odd causes for it, it is sometimes difficult and always interesting to try to figure out. One of the three factors involved in a situation such as this regards the source of bleeding. In this case there is no definite evidence of the source. Dr. Colby told me that cystoscopy showed clear urine from both ureters. We assume that the bleeding was coming from the right kidney, but actually that is an assumption rather than a fact. Recently we had a patient with bright-red blood spurting from the right ureter. An intravenous pyelogram showed a left ureteral calculus. If the bleeding had not been seen we would have assumed that it was coming from the left kidney. The only reasonable assumption here is that it was coming from the right kidney, which presumably was the mass in the right side.

As to the cause of the blood, assuming its source to be in the kidney, this was in all probability acute

surgical bleeding. There is no evidence of nephritis — no casts in the urine and nothing in the history to indicate blood dyscrasia. Of this surgical group there are three main causes, traumatic, inflammatory and neoplastic. There is no history of trauma and no evidence on the x-ray film of stone, and a traumatic origin is not likely. Many of the acute inflammatory bleedings are from a hemorrhagic type of cystitis. Dr. Colby tells me that the bladder was normal. Pyelonephritis of some type must be considered. Inflammatory bleeding usually is not of the profuse type that we see here. The bladder is ruled out, but certainly a tumor of the kidney, either cortical or pelvic, must be seriously considered.

In analyzing a few of the symptoms, we see that she did have an attack of acute pain in the costovertebral angle, which always brings up the probability of an obstructive lesion of some sort, which might be blood clot or primary hydronephrosis. Certainly, there was some obstruction. She had no evidence of fever or chills, to indicate an acute inflammatory condition as a probable cause of pain. The previous bleeding, of course, is somewhat in favor of neoplastic disease. It does not seem possible, however, that blood would occur from a neoplasm and not recur some time during the four-year period since she had had trouble. The bleeding from the vagina reported two weeks prior to entry is difficult to explain except on the basis of the vaginal examination, which showed a small mass in the posterior surface of the uterus, probably a small fibroid. There may have been others that caused bleeding. That is purely speculative. It does bring up the remote possibility of endometriosis. That is unusual in the kidney — probably it is more common in the bladder. Perhaps we cannot rule it out completely. On physical examination the mass in the right upper quadrant was not tender at the time of examination. Evidently, the acute obstruction that caused the pain had been to some extent relieved.

The laboratory work shows one interesting finding, a negative culture on the urine, with a few white cells and red cells. A negative culture in the presence of white cells or other evidence of infection always raises the question of tuberculosis. We have to have more evidence one way or the other to know whether this was present. That is not too important to answer so far as the acute difficulty is concerned, and apparently it was not something that entered the minds of the men in charge as a likely probability.

Will Dr. Wyman show us the x-ray films?

Dr. Stanley M. Wyman: The right kidney is fairly well outlined on the plain film. There is no evidence of stones. Intravenous dye appears promptly on both sides. Dilated calyxes are seen, and there seems to be definite thinning of the cortex of the kidney lateral to the dilated calyxes. What appears to be a large pelvis is also imperfectly outlined. Within the pelvis and all the calyxes there are multiple, round, rather smooth, lobulated, filling defects. The left kidney appears perfectly normal as far as can be seen.

Dr. Vose: In the standing position the right kidney drops well down below the iliac crest. Here is a kidney that was definitely hydronephrotic and undoubtedly had been for a good many months, probably years. The cortex is very thin. One can hardly see it, and this is something that does not take place in a short time as in an acute hydronephrosis. The filling defect may be a part of the cause of hydronephrosis, or it may be secondary to the hydronephrosis. My opinion is that it is secondary, that the hydronephrosis has been there for many years, and that the condition that caused the bleeding is of apparently recent origin.

This comes down to two or three conditions: tumor in the pelvis, nonopaque stone or hydronephrosis with secondary inflammation and bleeding with collection of blood clots in the kidney pelvis. There is also the outside possibility of tuberculosis. There is a little bit about the pyelogram that suggests a necrotizing papillitis, but she does not appear to have been ill enough to have that. There is no history of diabetes and not enough cortical necrosis to be consistent with that diagnosis. There is a possibility of some rare type of cyst in the kidney pelvis, but I think that tumor, nonopaque stone, and a blood clot are the most likely causes of the filling defects. It is almost a toss of the coin to determine which one. I would bet on primary hydronephrosis due either to intrinsic disease in the upper ureter or at the ureteropelvic junction or to a very low kidney with an abnormal implantation of the ureter with secondary infection and hematuria as my first guess, papillary tumor of the renal pelvis as my second, and nonopaque stone as the third.

Dr. Fletcher H. Colby: I think that Dr. Vose came as close as he could in this bizarre picture. Our preoperative diagnosis was papillary tumor of the renal pelvis. We decided that that was the most likely diagnosis in view of the fact that while this kidney had numerous rather large filling defects present in the upper portion, renal function was sufficiently well preserved so that the kidney excreted the dye in reasonably good concentration. Therefore, neoplasm involving the pelvis and not the parenchyma was more likely. The kidney was approached through a thoracoabdominal incision, and with that exposure the entire kidney and the renal blood supply were readily accessible. The kidney was enlarged, and the pelvis dilated, and through the pelvis one could feel round, rather soft masses. One of these masses was felt a little bit below the ureteropelvic junction. Believing that we were dealing probably with a primary tumor of the renal pelvis, probably papillary carcinoma,

we enlarged the incision and removed the entire kidney and ureter intact with a portion of the bladder wall.

Clinical Diagnosis

Papillary tumor of renal pelvis.

Dr. Vose's Diagnosis

Primary hydronephrosis, with secondary infection and hematuria?
Papillary tumor of renal pelvis?

Anatomical Diagnosis

Hamartoma of cloacal tissue in renal pelvis.

Pathological Discussion

Dr. Tracy B. Mallory: The specimen brought to the laboratory was entirely unlike anything that I had ever seen. The entire pelvis was filled with these polypoid masses, which had a myxomatous, almost gelatinous character. My thought was that

Figure 1.

they must consist of myxomatous tissue. The large tumor appeared to be attached to the renal pelvis in two spots, and there was an entirely separate tumor a short way down the ureter, which can be seen at the extreme left of the picture. When the microscopical sections came through they were most surprising and confusing. The tumor consisted of multiple acini of varying size embedded in an abundant fibrous myxomatous stroma. The acini were quite variable in character, some of them were lined with transitional epithelium of the usual type seen in the urinary passages, and others with obviously intestinal types of epithelium, some were clearly characteristic of Brunner's glands, others looked like small-bowel epithelium, with numerous Paneth cells present, and some looked like large bowel. None of the ordinary textbooks of pathology contain descriptions of such a tumor and in a long review of renal tumors by Melicow,[1] based on 199

Figure 2.

cases, nothing similar was reported. However, in the collection of material in the registry in the Army Medical Museum[2] they do have such tumors both in the bladder and in the renal pelvis. The explanation that has been offered and seems reasonable is that they arise from fetal nests of cloacal tissue. The cloaca of fetal life eventually separates and differentiates into the urinary passages anteriorly and the bowel posteriorly two ways, into intestinal epithelium or into transitional epithelium. That is I believe the most reasonable explanation of the tumor. I think it is entirely benign as far as one can judge from our usual microscopical criteria, and I believe that this other tumor part way down the ureter represents a second lesion of the same type rather than extension or metastasis from the renal tumor. It is difficult to know what exact name to attach to it. I would call it a hamartoma of cloacal tissue.

Dr. Colby: Quite a number of years ago we had a tumor in the bladder that histologically, as

far as I remember, was identical, or very nearly so, to this. It consisted of myxomatous tissue in which there were mucous secreting glands with no evidence of cancer. We classified it as an embryonic rest in a urinary bladder.

DR. MALLORY: Tumors similar to this can occur throughout the length of the urinary tract, in the bladder, ureters and pelvis of the kidney, and also can be found extending up the urachus even to the umbilicus.

DR. LAMAR SOUTTER: Will the tumor metastasize?

DR. MALLORY: I would not expect it to. It is such an unusual tumor that I am rather hesitant about being dogmatic about its degree of malignancy, but from the usual microscopical criteria I would not think it was malignant.

REFERENCES

1. Melicow, M. M. Classification of renal neoplasms: clinical and pathological study based on one hundred and ninety-nine cases. *J. Urol.* **51**:333-385, 1944.
2. Friedman, N. B., and Ash J. E. *Atlas of Genitourinary Pathology.* 215 pp. Washington, D. C.: Army Institute of Pathology, 1946. P. 18.

CASE 35222

PRESENTATION OF CASE

A forty-nine-year-old Italian housewife was admitted to the hospital because of an epigastric mass.

The patient's first admission to the hospital occurred twenty-three years before, when she gave a story of diarrhea and bloody stools of eighteen months' duration. Physical examination was not remarkable, but proctoscopy showed diffuse redness and ulceration of the mucous membranes as far as could be seen. A diagnosis of ulcerative colitis was made, and a double-barreled ileostomy was done, with considerable improvement. She continued to have occasional abdominal cramps and discharged bloody mucus by rectum for five or six years, but this gradually subsided until she was passing only a small amount of mucus by rectum every few weeks. The mucous discharge usually occurred during a cold. Eight years before the present admission she developed an empyema of the right chest following an unresolved pneumonia caused by Type III pneumococcus. Rib resection and drainage were required. Approximately two years prior to the present admission she noted a tight feeling and felt a lump just below the umbilicus. The mass did not increase in size during this period and produced no symptoms.

Physical examination revealed a well developed and well nourished, co-operative woman. The scar of the rib resection was well healed. There was a Grade II basal systolic murmur. The ileostomy in the right lower quadrant was in good condition. In the region of the umbilicus and extending to the left was a nontender, 5-cm. mass, which although slightly attached to the anterior abdominal wall seemed freely movable. The ileostomy located to the right and below the umbilicus functioned well. Pelvic examination was negative.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 85 diastolic.

The urine showed a specific gravity of 1.014 and was entirely normal. The hemoglobin was 10 gm., and the white-cell count 10,000. A barium enema could not be done because of the severe pain that it caused. Films of the abdomen and intravenous pyelograms showed a peculiar layer of calcification that was seen in a semilunar fashion to extend to the left of the upper lumbar spine and suggested the margin of the calcified tumor. The left kidney was normal in size and excreted the dye in good concentration. The right kidney was rather small and hypoplastic and showed delayed excretion with rather wide calyxes and pelvis filling one or two hours after the injection of dye. The right ureter was not well visualized. There was a suggestion of a mass in the right side of the pelvis and right side of the abdomen. A chest film showed some elevation of the right leaf of the diaphragm, with pleural adhesions that caused slight limitation of motion. There were old partial resections of several right ribs. There was some fibrosis, and increased markings in both lungs, mostly on the right. There was some thickened pleura over the right chest laterally. The heart shadow was not enlarged, but there was rather marked tortuosity of the aorta.

After preparatory transfusions an operation was performed on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES G. MIXTER: This type of exercise is interesting and sometimes amusing to the audience but puts the discusser on the hot seat because there is a cat in the meal somewhere. I am sure that there is a festive feline lurking around here that is going to get me into trouble. "Films of the abdomen and intravenous pyelograms showed a peculiar layer of calcification. . . ." I suspect that that may be the cat in the meal.

We might make a brief review of the past history to see if we can find anything that might have a bearing on this patient's mass. In the first place she was an Italian, of about fifty years, and she had a history of ulcerative colitis that ran a more or less characteristic course requiring operation, and then presumably the large bowel quieted down and had remained more or less quiescent. That I think we should put aside for future discussion because it might have some bearing on the differential diagnosis. I believe we can forget about empyema following an unresolved pneumonia as far as the differential diagnosis is concerned, because I do not see how this would have any bearing on the mass at the umbilicus. It is true occasionally, and I have seen it in children, that a chronic empyema may

descend through the diaphragm and find a point at the umbilicus, but this case certainly would not fall in that category.

The next thing to discuss is the abnormality of the kidney. The mass was on the left. The right kidney was a hypoplastic type of kidney with delayed excretion, and yet the urine was normal without anything of consequence in the sediment. That to my mind perhaps suggests a hypoplastic kidney, possibly of congenital origin, and I do not believe has anything to do with this picture. We might consider some retroperitoneal mass from the wolffian ridge, but this being on the right side and the tumor on the left makes it unlikely. Furthermore it presumably was attached to the anterior abdominal wall.

Perhaps it is all right to ask if a blood Wassermann or Kahn test was negative. Also, I should like to know about the gastrointestinal series, the gallbladder studies or lateral films and whether the patient had a peritoneoscopy.

Dr. Tracy B. Mallory: At the first entry, twenty-two years previously, the blood Wassermann test was negative. Dr. Wyman can show the x-ray films at any time.

Dr. Mixter: I would like to see them. The patient had tortuosity of the great vessels, and, of course, we have to consider in the differential diagnosis an aneurysm but it is hard to link that up with slight fixation of the anterior abdominal wall. Certainly, no mention is made of pulsation.

Dr. Stanley M. Wyman: The chest films show the old defects in the right ribs, old pleuritis and a somewhat tortuous thoracic aorta. I can see no evidence of active disease in the chest. There are a few scars in the right-upper-lung field, which are possibly due to old tuberculosis. The calcification described lies in linear fashion, is somewhat lobulated, is situated just to the left of the third lumbar vertebra and extends over a distance of perhaps 5 or 6 cm. The right kidney shadow can be seen: it is very small. The left kidney is long and rather slender.

Dr. Mixter: I believe that the calcification has considerable bearing on the differential diagnosis.

Dr. Wyman: The later films from the pyelogram show the very small right kidney to have excreted a small amount of dye of poor concentration at the end of two hours and the calyceal system is greatly dilated, suggesting possibly an old infectious process. There is some soft-tissue density in the right pelvis, which is hard to define accurately but is present on all films. I am unable to say what it is. I cannot define it very well, but it may be linked up with this trouble in the right kidney.

Dr. Mixter: What is this shadow?

Dr. Wyman: The lower margin of the liver.

Dr. Mixter: Is there any gross deformity of the bladder?

Dr. Wyman: The bladder seems to have a fairly normal contour. How much of the shadow in the right abdomen is due to the ileostomy, I do not know.

Dr. Mixter: The pelvic examination was reported negative. That, however, does not necessarily rule out a pedunculated mass.

Let us take a brief survey of the possibilities. In the first place I think that we can rule out any acute infection. The temperature, the patient's general condition and the duration of the illness over a period of two years are against anything of that nature. Furthermore, I think we can rule out cancer in all probability because the condition was stationary over two years. The patient did not show the inroads of a malignant process, although we have to bear in mind that carcinoma is a fairly frequent complication of ulcerative colitis — much more so than in the normal bowel. I believe we can rule that out also.

That boils it down pretty much to consideration of possible masses in the umbilical region. Let us first consider the masses that do not necessarily or frequently show calcification, because although that is suggestive it may lead us astray. The first one that comes to mind is the leiomyofibromatous type of tumor of the gastrointestinal tract; even a gastric tumor that has grown outward from the serosal surface might be located in this position, and sometimes remains very quiescent. But I still believe that this calcification is of sufficient importance so that I would not consider that diagnosis.

Fecal masses should be considered in all differential diagnoses, but here is a woman who had had an ileostomy. Fecal masses almost invariably occur in the large bowel. Continuous pressure over a fecal mass will cause indentation almost invariably. We have none of the obstructive signs that would be present with a fecal mass, and it certainly would not persist over a period of two years. There are rare tumors, especially urachal cysts that occur below the umbilicus and are attached to the abdominal wall, it is true, but they are not freely movable. I think from the mobility of this tumor we can rule out any lesion within the anterior abdominal wall or anything too intimately in contact with it. There are omental and mesenteric cysts. It is true that all cysts may deposit a certain amount of calcium, and that may be true of omental and mesenteric cysts, but in my personal experience I have never encountered it and I believe it must be rare to find calcium deposits in such cysts. It is true that my experience was almost exclusively in children, in whom one would not expect to find calcareous deposits perhaps. They are silently growing and are generally brought to one's attention simply as an abdominal mass. They are freely movable, except when they reach enormous size, as particularly the mesenteric cysts. They usually occur in the upper small bowel, and often are dumb-

bell in shape. Pancreatic cysts and liver cysts, particularly pancreatic cysts, may form calcareous deposits, but one would expect fullness in the epigastrium; certainly that is true of simple cysts of the liver. I have seen one simple cyst of the liver that presented as a definite epigastric mass, which descended on respiration, and it would not fit into this category. It is true that Meckel's diverticulum can attain enormous size, but it is not palpable except when it is accompanied by acute inflammatory reaction or perforates and forms an abscess. So there again I think we can rule that out. Let us now consider tumors that may be associated more commonly with calcification. First let us consider calcified mesenteric glands. Here we have, however, central foci that do not show a crescentic linear type of calcification that we see here. Furthermore, a gland of this size would certainly be unusual. Perhaps we should mention lithopedium, although the x-ray appearance would be different, and I think that is a far-fetched possibility. We have to consider echinococcal cyst; a wandering cyst might be located in this region. It is not uncommon to get a linear calcification, and this woman was an Italian. There is no record of a complement-fixation test available.

Hematomas may show calcification — although the calcification is usually more or less fuzzy and diffuse rather than linear.

A gallstone may be palpable, and I have here one that I removed some years ago. It is an interesting specimen and was readily palpable. I could move it about the abdomen. It made a perfect cast of the gall bladder. In the case under discussion one would have to suppose that it had ulcerated through the gall bladder, wrapped itself in the omentum and worked its way down to the umbilicus. The calcium deposit on the surface could well follow this type of shadow. I think that is far fetched. Calcification is frequently associated with any form of chronic abscess or infection.

One thing we must consider is a pocket in the old ulcerative colitis that she had years previously, with a chronic abscess as well as calcification. We cannot rule it out. We have to consider other likely diagnoses.

I do not believe this was a foreign body lying within the intestinal lumen. It is true the human being is capable of all sorts of aberrations, and any cavity within the body may be a suitable receptacle for a foreign body. Some of us have seen hairpins introduced into the female bladder, and I have taken a rivet out of the male bladder. But a foreign body introduced through an ileostomy would probably not stay in the intestine for nearly two years without either being extruded or causing difficulty. On the other hand this patient was operated on twenty-three years before this admission. I do not know what the sponge-count report was, but one of the things I have strongly in mind is that she had a sponge wrapped up in the omentum that caused this linear calcification such as we see in this film. Sponges can lie quiescent for years. I have removed one that was a movable mass in the abdomen, in a woman who had had an ovarian cyst removed some three or four years before. The sponge had rolled itself up in the omentum and lay dormant over that period. A sponge can show calcification of this type.

Another calcified tumor that we must consider is uterine fibroid, pedunculated, or one that from torsion had separated by necrosis and then become engrafted at some other site, perhaps near the umbilicus. Such tumors may show calcification of this type. Another definite possibility is a pedunculated ovarian cyst, because ovarian cysts are prone to show a fine linear calcification. I think I am right on that from the x-ray standpoint.

DR. WYMAN: Sometimes.

DR. MIXTER: Particularly the dermoids have calcification that might follow this pattern.

Time is drawing to a close and I must end my discussion, but I would say that there are three diagnoses I would particularly like to consider as possibilities. I do not believe I would want to commit myself any further than that. On the law of chances I would say first that this might be a foreign-body cyst; second, a dermoid; and third, a fibroid. I believe the time is up, and as the old saying goes you never can tell what is in the box before you take the cover off. I would like to know what operation showed.

DR. MALLORY: Dr. Warren, will you tell us your opinion and operative findings.

DR. RICHARD WARREN: Our reasoning was not so astute as Dr. Mixter's. We had however more information that I am afraid did not get into the record. There were two or three points that swayed us. The first was that the patient had not had any passage of material by rectum for several years. The record states that there was mucus passed every few months but that was inaccurate. The

second point was that rectal examination was impossible because there was a complete block at the internal sphincter. Tying these facts together with the mass that was palpable in the region of the umbilicus we began to think this was inspissated material — accumulated colonic secretions. We could not explain the calcification. That bothered us a great deal.

Clinical Diagnosis

Inspissated material in colon.

Dr. Mixter's Diagnosis

Cyst, due to foreign body.

Anatomical Diagnosis

Mucocele of large bowel due to strictures in ulcerative colitis of defunctioned bowel.

Pathological Discussion

Dr. Warren: We operated on the patient and found that she did have a greatly distended right colon — greatly distended with a mucoid type of material. The defunctioned terminal ileum was also distended to the same diameter as the colon. The material was under such tension that it was oozing out through the interstitial spaces. Most of it was in the right colon, although there were patches on the left side as far down as the lower segment. This material was incarcerated in several compartments. The lumen of the colon at the rectal end was closed off as it was at the defunctioned end of the double-barreled ileostomy. It was interesting also that the patient had had acriflavine colonic irrigation for a year or so following ileostomy.

Dr. Mixter: I am surprised there was not a palpable, putty-like mass in the right side of the abdomen.

Dr. Mallory: This picture shows the entire colon here and the terminal portion of the ileum, which, as one can see, is dilated almost to the size of the colon. The next picture shows the bowel after it was opened, and here is one of these huge masses of inspissated secretion. As one passes along to the sigmoid there is another mass of mucus, not quite so large. The mucus, as Dr. Warren said, had partially split the wall of the bowel so that we found mucus all through the layers of intestinal wall. This caused us considerable worry at first for fear we were dealing with colloid carcinoma, in which tumor cells may be very infrequent and one finds only great masses of mucus. Here and there, however, we could find remnants of intestinal epithelium, which were quite normal — not neoplastic in character. So I think this was clearly a mucocele of the large bowel resulting from multiple foci of obstruction.

Dr. Mixter: Was there any true calcification?

Dr. Mallory: We were not able to identify the calcification.

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PUBLIC HEALTH AND MENTAL HEALTH

Mystery and abstruseness continue to be associated with psychiatry and psychotherapy by people who know little about the subjects and by some who professedly know much about them. It is questionable whether the encouraging of awesome respect for this branch of medicine will do much toward advancing it on a sound basis.

An instance of comparative simplicity in concept and in teaching some of the principles of psychiatry is presented in a recently published pamphlet.* This pamphlet is the report on "An Institute on Mental Health in Public Health" held by the California State Department of Public Health and The Commonwealth Fund last July. The Institute was attended by 27 health officers, and the teaching and discussion were conducted by 8 psychiatrists, 3 pediatricians with psychiatric training and 5 public-health leaders.

With the new impetus being given to the psychiatric implications in almost all human pursuits, it is understandable that the sphere of public health should be included in psychiatry's ambit. According to the pamphlet — a more comprehensive account is to be issued later — the Institute touched on many topics in its clinics, lectures and discussions, but its chief work and accomplishment was an inquiry into the understanding of "interpersonal relationships."

Health officers and health departments deal primarily with the prevention, amelioration and cure of disease. Concentration on the pathologic process is apparently the principal concern. The individual, with his particular personality, who has or may acquire the disease is considered secondarily or perhaps not at all. The Institute, in its daily meetings, revealed to its student members that it is people who have diseases, people with their fears, resentments, social, economic and emotional problems. It is an old story — the best care *of* the patient is care *for* the patient. Also, it seemed to become clear or clearer to the students that their own attitudes and personality problems could too frequently produce blind spots in their associations with other human beings, both patients and colleagues.

The pamphlet states: " . . . unless the health officer listens to the patient he cannot learn enough about the patient to know how to deal with him skillfully, and unless the health worker enters into a feeling relationship with the patient his advice and his questions are both likely to be fruitless." This is such a simple and apparently uninspiring conclusion that it may seem surprising and even disturbing that supposedly mature, intelligent public-health officers were pleased and delighted with the course.

It may well be that the students benefited from the opportunity to listen to and to discuss points and subjects that are relevant to what makes everyone tick. The "what," as described in the pamphlet,

*Smith, G. *Human Relationships in Public Health: Report of institute on mental health in public health.* 18 pp. New York: The Commonwealth Fund, 1949.

was not founded on disputable and unproved Freudian and neo-Freudian dogmas. That credits the teachers with perspective and wisdom.

Science will do better than it has to date if it proves anything more fundamentally constructive than the Golden Rule. A tip to science might be to extirpate self-interest in man without destroying or nullifying his constructive, altruistic energies.

AMERICAN BOARD OF PREVENTIVE MEDICINE AND PUBLIC HEALTH, INC.

THE establishment of the American Board of Preventive Medicine and Public Health represents a significant step in medical progress. The Board, which is sponsored by the American Medical Association, American Public Health Association, Association of Schools of Public Health, Southern Medical Association and Canadian Public Health Association, has adopted requirements for certification that are in harmony with those of the various specialty boards previously set up: general qualifications, such as satisfactory moral and ethical standing in the medical profession; adequate medical training and internship in an approved hospital; and licensure to practice medicine in the United States. To be eligible for examination, applicants must also have had special training and experience in preventive medicine and public health for at least six years after internship (special academic training, or its equivalent, and field training or residency of at least two years of field experience in general public-health practice, including planned instruction, observation and active participation in a comprehensive, organized public-health program); each person to whom a certificate is issued must limit himself to the teaching or practice of public health as a specialty. Provision is made for the certification, without examination, of the Founders Group, consisting of practitioners of preventive medicine and public health who have achieved unquestioned eminence either in an academic status or through practical achievement in positions of responsibility. The standards thus set up appear to guarantee that diplomates of the new board will be men of the highest caliber in their field.

The newly recognized specialty is a matter of great interest to all physicians, since it is, in essence, the medical profession's answer to the challenge of providing adequate medical care on two crucial levels of medical practice. The setting up of the Board may be regarded as a forward step toward the goal of giving to every person "the basic essentials, diagnostic, preventive and therapeutic measures that will enable him to enjoy a more productive life and become a greater asset to the community."* The significance of progress in this vital field, which has for years been the battleground between the proponents of free practice and those who demand state control, is obvious.

*Getting, V. A. Public health today and tomorrow in Massachusetts. *New Eng. J. Med.* **239**: 295-298, 1948.

NEW DIRECTOR OF MASSACHUSETTS GENERAL HOSPITAL

IN THE selection of a director to succeed Dr. Nathaniel W. Faxon, who is retiring after twenty years of distinguished service, the trustees of the Massachusetts General Hospital have again demonstrated the excellent judgment that usually characterizes their decisions.

Dr. Dean A. Clark, who will shortly assume the directorship of the hospital, is a native of Minnesota, a graduate of Princeton University and holder of the degrees of bachelor of arts and bachelor of science in physiology from Oxford University, where he studied three years as a Rhodes Scholar. He received his medical degree from The Johns Hopkins University School of Medicine in 1932, after which he served an internship in medicine at the Johns Hopkins Hospital. He then became assistant resident in medicine and neurology at the New York Hospital; National Research Council fellow in neurophysiology at the Cornell University Medical College; intern at Phipps Psychiatric Clinic, in Baltimore; and intern at Trudeau Sanatorium, in Trudeau, New York.

In 1938 and 1939 Dr. Clark made a survey of group medical practice and medical service prepayment plans in various parts of the country. In the latter year he became a commissioned officer in the reserve corps of the United States Public Health Service, and for the next several years was en-

gaged largely in studies of the organization and administration of medical care programs. From 1941 through 1948 Dr. Clark also lectured or conducted courses on medical economics and the distribution of medical care in several colleges and universities. He is at present associate professor of public-health practice at Columbia University College of Physicians and Surgeons and lecturer in medical economics at the School of Public Health of the University of California. Since August, 1945, Dr. Clark has been on leave of absence from the Public Health Service devoting his time to the medical direction of the Health Insurance Plan of Greater New York.

DEAN A. CLARK, M.D., B.Sc. (Oxon.)

Dr. Clark obviously brings to this important post a wide experience and unquestioned talent in medical organization and administration. In these times when new and better ways are being sought through which to deploy the services of medicine, expert guidance is needed in every area. The Massachusetts General Hospital is to be congratulated on having found such an able successor to its long line of illustrious administrators.

BIOLOGIC ENIGMA

MANY mysteries of the animal kingdom, according to a feature story released by the University of Wisconsin News Service, remain unsolved, although ardent naturalists have spent years in their investigation.

Thus it is not known why the Scandinavian lemmings make their periodic marches into the sea, why ocean salmon return to their home streams to spawn, nor, parenthetically, why the north Atlantic whale, with thousands of miles in which to roam, picks Cape Cod, Massachusetts, as a place to drive himself irreversibly ashore. The residents of that famous resort would like to know.

The Wisconsin scientists, intrigued by these biologic enigmas, have turned their attention to the migratory habits of bats, with particular reference to the locations that they select for their winter hibernation. Banding expeditions have been conducted in the abandoned mines, the caves and deserted houses of northern Wisconsin, but the bats discovered have been far fewer than those known to inhabit the region in the summer, and have been mostly males. When the search is extended, the belfries of the countryside will not be overlooked.

In the summer, females are discovered in great numbers in the local attics, where they bear (perhaps in place of gifts) their young. Apparently the hibernating males, despite their bachelor habits, have found an answer to the question (a sign of good breeding), "Shall we join the ladies?"

More light is shed on the same problem by the discovery that bats may be divided into two types: the social, who hibernate in colonies and presumably join the ladies, and the nonsocial, — the Chiropterous counterparts of the lone wolf and the bank beaver, — who, shunning the stag lines, are rarely found in groups and may migrate to distant climes in winter.

Perhaps the work with banding, Wisconsin News Service volunteers, will solve this mystery of the missing bats.

NOTES FROM THE MEDICAL EXAMINER

DEATH DUE TO CONFLAGRATION

Approximately 10,000 deaths per year in the United States are caused by burning or by other lethal attributes of conflagrations. In almost a quarter of these the victim is found dead at the scene of the fire. Such deaths are investigated by the medical examiner or coroner. Although the majority are due to the fire and are accidental, this is not invariably the case. Willful destruction of a dead body by fire may be an attempt to perpetrate an insurance fraud or to conceal a homicide. It is the purpose of this communication to review briefly the effects of conflagrations that are most frequently responsible for death on the premises and to discuss certain post-mortem characteristics of burned bodies that are likely to be of medicolegal importance.

One or several factors may be responsible for death during and because of a conflagration. Usually, smoke is inhaled before there is significant exposure to heat, and frequently the victim is unconscious or dead before there has been burning of the skin.

Although the composition of smoke varies enormously according to the type of fuel, the amount of oxygen available to support combustion, the temperature attained, and the extent to which the smoke has been diluted with air it almost invariably contains a dangerous amount of carbon monoxide. In a smoke-filled room the concentration of this gas is often so great as to cause loss of consciousness within a few minutes. In the case of smoldering fires dangerously high concentrations of carbon monoxide may be present in air that has so little visible smoke that it is erroneously regarded as safe to breathe. Even though the amount of carbon monoxide is not excessive carbon dioxide may be present in a concentration high enough to cause rapidly fatal asphyxia. Rarely is the oxygen content of smoke so low as to result in oxygen starvation.

If neither the carbon monoxide nor the carbon dioxide content of the smoke is high enough to cause asphyxia, various irritating combustion products may cause suffocation owing to rapidly developing edema of the air passages or lungs. Irritants contained in smoke derived from organic materials likely to be burned in an ordinary fire include acetic acid, aldehydes, ammonia, formic acid, furfural, pyroligneous acids, resins, saturated and unsaturated hydrocarbons and tar. Superheating of fats and certain oils causes the formation of highly toxic acrolein. Hydrogen cyanide and sulfide are both liberated in large amounts in the burning of wool. Highly irritating anhydrides of nitrogen are generated by the burning of various plastic and synthetic nitrocellulose compounds. All these combustion products are injurious to the respiratory membranes and are capable of causing rapidly obstructive edema.

Failure to find evidence of smoke inhalation in the body of a person found dead at the site of a conflagration should lead to the suspicion that death occurred before the fire started. If the victim was alive and breathed smoke, carbon is usually present in the medium and small bronchi in amounts sufficient to cause a gray or gray-black discoloration. Usually, chemical irritants in the smoke cause an outpouring of mucus and the development of an intense hyperemia of the mucous membranes. As a rule the carbon monoxide content of the blood is significantly elevated.

It is true that some of the victims who die at the site of a conflagration do so because of burning when circumstances are such that fatal burning takes place before sufficient smoke has been inhaled to cause asphyxia or unconsciousness. Extensive and severe burning of the surface of the body may result in rapidly fatal circulatory failure because of peripheral vascular collapse and shock. If the victim is sufficiently close to flame to receive burns of the face the inhalation of heat may cause thermal injury of the larynx, with fatal laryngeal edema.

It is sometimes desirable to appraise cutaneous burns in terms of whether they were received before or after death. Fluid-filled blisters in association with cutaneous burning indicate vital reaction, unless putrefaction has started. If putrefaction has begun vesication may be a post-mortem artifact. Another artifact frequently encountered is the steam blister. When skin is superheated, whether it is live or dead, sufficient steam may be generated beneath an intact epidermis to cause it to become elevated. Such blisters either rupture immediately or collapse as soon as the skin cools and never contain fluid. The finding of a zone of edema and hyperemia at the junction of burned and unburned tissue is evidence of vital reaction. Although recognition of vital reaction establishes the fact that burning occurred during life, its absence does not necessarily exclude the possibility of ante-mortem thermal injury. Burning that began before death may be completely obscured by the continued application of heat after death.

The continued application of heat after death may cause the skin to contract and split with the formation of deep fissures that to the inexperienced observer resemble knife wounds. Protracted exposure of the dead body to intense heat causes the extremities to flex and to assume curiously distorted attitudes. The bones of a badly burned body become so brittle that they can be broken by the stream of water from a fire hose or in the removal of the body from the place of the fire. If the neck is badly burned the laryngeal cartilages often warp in such a manner as to occlude the airway. The hyoid bone may become so fragile as to break on manipulation.

Expansion of the intracranial contents by heat may cause the cranial sutures to separate and the calvarium to fracture in an explosive manner. Such thermal changes in the skull are often accompanied by massive epidural extravasation of blood from the great venous sinuses. Unless there is unmistakable external evidence of violence to the head the diagnosis of ante-mortem head injury in a case of a badly burned body should be made with great caution. The finding of subdural or subarachnoid bleeding or cerebral contusion or laceration may be prerequisite to recognition that skull fracture was probably ante mortem and due to physical violence rather than to heat.

No matter how badly burned the body, an adequate post-mortem examination may provide information to identify the dead person, to determine the time of death in relation to that of the fire and to establish the cause and manner of death. The physical characteristics of the body may not be consistent with those of the person it is supposed to represent. Death may have resulted from some other cause before the fire. It may be found that the decedent perished by fire because he was incapacitated by antecedent disease, injury or intoxication.

ALAN R. MORITZ, M.D.
Professor of Legal Medicine
Harvard Medical School

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PROGRAM FOR PREMATURE INFANTS

The program for the care of premature infants, established by the Division of Maternal and Child Health of the Massachusetts Department of Public Health in 1937–1938, was the first state program in the United States. At that time state-wide publicity was provided. During the ensuing years there have been many changes in local medical, nursing and board-of-health personnel so that it seems advisable again to outline the program in order that all concerned with the care of the premature infant may be cognizant of the facilities available for their care.

At the beginning of the program 48 hospital centers outside Boston adequately equipped to care for premature infants were established on a geographic basis so that infants born outside these centers would have a relatively short distance to travel for care.

Since then the licensing of hospitals has come into the Department of Public Health, with resulting improvement in standards of nursery care in many hospitals having maternity service other than the original centers. There are also in the city of Boston several hospitals equipped for care of premature infants brought in from outside areas.

In 1937 and 1939 legislation was passed allowing for transportation, if requested by physician and parent by the local boards of health, to hospitals equipped for care and for payment of reasonable hospital expenses of such infants by local boards of welfare when parents need such help without the parents' being deemed on public relief.

To facilitate these services the physician delivering the premature infant in the home is required by law to report such a delivery by telephone as soon as possible, and also in writing within twenty-four hours to the local boards of health and welfare. For premature infants born in the hospital the hospital superintendent is responsible for reporting to the local board of welfare of the town where the infant was born. The board of welfare of the town of settlement will reimburse the board of welfare of the town where the infant was born for hospitalization, provided the expense is incurred within ten days prior to the notice.

Thus, Massachusetts has made provision for reporting of all premature births, for transportation and for payment for hospitalization of the premature infant, and a group of hospitals is equipped to give adequate care.

The facilities for transportation and hospitalization appear to be the factors in the program that are least well known by physicians. It is thus the purpose to endeavor to bring these to the attention of the readers of the *Journal*. A number of hospitals have transportation facilities in the form of heated ambulances and baskets or cases for carrying premature infants that will keep the baby warm in transit. It is suggested that physicians make inquiries of the hospital, board of health or visiting-nurse association in the towns in which they practice regarding the methods of obtaining this service in emergency. It is further suggested and even urged that the premature infant be transported to the *nearest* hospital adequately equipped for care instead of being subjected to a long journey to a distant center. This may prevent infant deaths. It would be advisable to telephone to the hospital of choice in advance to ensure admission of the patient and to obtain any transportation facilities that the hospital is able to provide.

In 1947 a series of regional institutes for hospital administrators were conducted for the discussion of hospital nursing standards. Standards for care of the premature infant were included.

Before the war a refresher course was provided for all nursery supervisors in the hospital centers. Changes in personnel have occurred, and refresher courses are now being given again to new nursery supervisors; 26 nursery supervisors will have completed this course by July 1. It is planned to continue these courses until all are accommodated.

In communities where public-health nursing service in the field of infant-health supervision is available, help can be given to the mother after the

infant leaves the hospital. Under the supervision of the physician the public-health nurse will help the mother to prepare for the baby's homecoming. She will also demonstrate bathing and other care recommended by the physician and will make periodic visits to the home and progress reports to the physician. This is a good preventive health measure and also gives the mother confidence in caring for her baby. When such assistance is desired the physician or the hospital should notify the public-health nurse of the date of discharge as far in advance as possible.

FLORENCE L. MCKAY, M.D.
Director, Division of Maternal and Child Health

DIRECTIONS FOR IMMEDIATE CARE OF PREMATURE INFANTS

The Massachusetts physician who delivers a premature infant in one of the approved hospitals listed in Table 1 will have full physical and nursing facilities at hand for the baby's care. Should a physician be present at or called in after a premature delivery in another hospital or at the mother's home, his primary responsibilities are to keep the infant under the best possible circumstances until it is admitted to an approved nursery, and to see that this admission is promptly accomplished.

TABLE 1. *Hospital Centers for the Care of Premature Infants with Equipment and Routines Approved by the Massachusetts Department of Public Health.*

LOCATION	HOSPITAL
Southeastern District:	
Attleboro	Sturdy Memorial Hospital
Fall River	Truesdale Hospital
	St. Anne's Hospital
Barnstable	Cape Cod Hospital
Nantucket	Nantucket Hospital
New Bedford	St. Luke's Hospital
Oak Bluffs	Martha's Vineyard Hospital
Taunton	Morton Hospital
South Metropolitan District:	
Framingham	Framingham Union Hospital
Quincy	Quincy City Hospital
Weymouth	South Shore Hospital
North Metropolitan District:	
Cambridge	Mount Auburn Hospital
Malden	Malden Hospital
Newton	Newton-Wellesley Hospital
Waltham	Waltham Hospital
Northeastern District:	
Beverly	Beverly Hospital
Haverhill	Haverhill Municipal Hospital
Lawrence	Lawrence General Hospital
Lynn	Lynn Hospital
Melrose	Melrose Hospital
Salem	Salem Hospital
	North Shore Babies Hospital
South Central District:	
Worcester	Worcester City Hospital
	Worcester Memorial Hospital
	St. Vincent Hospital
North Central District:	
Clinton	Clinton Hospital
Fitchburg	Burbank Hospital
Gardner	Henry Heywood Memorial Hospital
Leominster	Leominster Hospital
Lowell	Lowell General Hospital
	St. John's Hospital
Connecticut Valley District:	
Greenfield	Franklin County Hospital
Holyoke	Holyoke Hospital
	Providence Hospital
Montague	Farren Memorial Hospital
Northampton	Cooley Dickinson Hospital
Springfield	Wesson Maternity Hospital
	Mercy Hospital
Westfield	Noble Hospital
Berkshire District:	
Great Barrington	Fairview Hospital
North Adams	North Adams Hospital
Pittsfield	St. Luke's Hospital
	Pittsfield General Hospital

The immediate care of the infant should be largely a matter of ensuring warmth and protection from potential sources of infection. The only word necessary regarding feeding is a warning against any attempts in that direction until the baby has been placed under proper nursing care and environment, and even then a day or two without feeding is recommended.

TABLE 2. *Other Hospitals Equipped to Care for Premature Infants Brought in From the Outside.*

LOCATION	HOSPITAL
South Metropolitan District:	
Brockton	Goddard Hospital
	Brockton Hospital
North Metropolitan District:	
Boston	Allerton Hospital
	Boston City Floating
	Boston Floating Hospital
	Carney Hospital
	Children's Medical Center — Infant's Hospital
	Faulkner Hospital
	Massachusetts General Hospital (Vincent Building)
	New England Hospital for Women and Children
	Sancta Maria Hospital
Cambridge	Cambridge City Hospital
Concord	Emerson Hospital
Medford	Lawrence Memorial Hospital
Northeastern District:	
Amesbury	Amesbury Hospital
Ipswich	Cable Memorial Hospital
Woburn	Charles Choate Memorial Hospital
South Central District:	
Southbridge	Harrington Memorial Hospital
Worcester	Hahnemann Hospital
North Central District:	
Lowell	St. Joseph's Hospital
Berkshire District:	
Adams	Plunkett Memorial Hospital

Warmth should be a matter of seeing that the body temperature does not fall after birth rather than of applying heat once the baby becomes cold. Any covering that is clean, soft and prevents heat conduction is satisfactory. A sterile towel, or, failing that, a clean towel, wrapped about the body and scalp, with several thicknesses of soft blanket wrapped over towel and infant, is ideal. A hemostat may be left on the cord until a proper tie can be applied in the nursery to which the infant is sent. Thus covered, the infant may be laid near a radiator or stove or in whatever warm area is available. Serious burns may result from the hasty use of hot water bottles, which should not be needed if the procedures mentioned above are performed expeditiously.

Protection from infection means, mainly, protection from people. Speed in removal to a proper premature nursery will accomplish this and better than will any other activity. It may here be stated that these infants have remarkable powers of survival for the first several hours after birth, so that it is usually not necessary that they be frequently unwrapped or otherwise disturbed for inspection.

A list of hospitals with nurseries properly equipped and staffed for care of premature infants is presented in Table 2. It should be possible to trans-

port an infant born anywhere in Massachusetts to one of these hospitals within less than an hour. Most of them have, or have access to, an artificially heated carrier, which can be placed in any automobile and sent out as a "premature ambulance." Plans are now maturing for the provision, by a generous donor, of such an "ambulance" wherever a survey now in process demonstrates that one is clearly needed. Most of those in present use have a connection by which they can be converted into oxygen chambers by the attachment of a portable oxygen tank.

All the physician need do is to telephone the nearest approved hospital at once, give details and arrange a plan by which the ambulance may be sent out. This often means dispatching the infant's father or other relative in a car or taxicab. The hospital can be warming the ambulance until his arrival, and not only should send the ambulance and oxygen with him but also should provide a nurse or house-staff member to watch over infant, ambulance and oxygen on the return journey. Since we have occasionally seen infants arrive at our own hospitals in supposedly oxygenated carriers in which no one had bothered to turn on the oxygen tank, the doctor may well make sure that those accompanying the baby to the hospital know how to use their equipment. He should also see to it that a proper history, or a person able to give such a history, accompanies the infant.

A word may be added about vitamin K and stimulants. Nothing of importance will be lost if the former is not administered till the infant arrives at the nursery where he is to be cared for. Stimulants are seldom called for and, unless given by those familiar with the care of premature patients, might often better be avoided. If the infant's condition is rapidly failing and there is unavoidable delay in his admission to an approved nursery, caffeine sodium benzoate, ¼ gr. (16 mg.), may be given intramuscularly, and repeated once if no improvement has occurred at the end of fifteen minutes.

This section was prepared by the Massachusetts State Committee on the Fetus and Newborn of the American Academy of Pediatrics.

Dr. W. Bradford Adams, Springfield
Dr. Fred H. Allen, Holyoke
Dr. Joseph Garland, Boston
Dr. Paul J. Jakmauh, South Boston
Dr. Robert T. Moulton, Salem
Dr. Alfred S. O'Connor, Worcester
Dr. Herman C. Petterson, Boston
Dr. Stuart F. Stevenson, Boston
Dr. Alfred Weller, Arlington Heights
Dr. Clement A. Smith, Boston
Chairman

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Autobiography of Benjamin Rush: His "Travels Through Life" together with his Commonplace Book for 1789–1813. Edited with introduction and notes by George W. Corner, M.D., 8°, cloth, 399 pp., with 8 illustrations and frontispiece. Princeton, New Jersey: Princeton University, 1948. $6.00.

NOTICES

AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWSHIPS

The American College of Physicians announces that a limited number of fellowships in medicine will be available from July 1, 1950, to June 30, 1951. These fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $2200 to $3200.

Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania, and must be submitted in duplicate not later than October 1, 1949. Announcement of awards will be made in November, 1949.

(*Notices concluded on page xvii*)

When ordering needles cisternal,

Books, sponges or doses diurnal,

Dr. Wise always mentions

(Or has those intentions)

***The ads that he reads in the* Journal.**

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